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Section Application Domains

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ANTIQUÉ Project-Team

4. Application Domains

4.1. Verification of safety critical embedded software

The verification of safety critical embedded software is a very important application domain for our group. First, this field requires a high confidence in software, as a bug may cause disastrous events. Thus, it offers an obvious opportunity for a strong impact. Second, such software usually have better specifications and a better design than many other families of software, hence are an easier target for developing new static analysis techniques (which can later be extended for more general, harder to cope with families of programs). This includes avionics, automotive and other transportation systems, medical systems ...

For instance, the verification of avionics systems represent a very high percentage of the cost of an airplane (about 30 % of the overall airplane design cost). The state of the art development processes mainly resort to testing in order to improve the quality of software. Depending on the level of criticality of a software (at the highest levels, any software failure would endanger the flight) a set of software requirements are checked with test suites. This approach is both costly (due to the sheer amount of testing that needs to be performed) and unsound (as errors may go unnoticed, if they do not arise on the test suite).

By contrast, static analysis can ensure higher software quality at a lower cost. Indeed, a static analyzer will catch all bugs of a certain kind. Moreover, a static analysis run typically lasts a few hours, and can be integrated in the development cycle in a seamless manner. For instance, **ASTRÉE** successfully verified the absence of runtime error in several families of safety critical fly-by-wire avionic software, in at most a day of computation, on standard hardware. Other kinds of synchronous embedded software have also been analyzed with good results.

In the future, we plan to greatly extend this work so as to verify *other families of embedded software* (such as communication, navigation and monitoring software) and *other families of properties* (such as security and liveness properties).

Embedded software in charge of communication, navigation, and monitoring typically relies on a *parallel* structure, where several threads are executed concurrently, and manage different features (input, output, user interface, internal computation, logging ...). This structure is also often found in automotive software. An even more complex case is that of *distributed* systems, where several separate computers are run in parallel and take care of several sub-tasks of a same feature, such as braking. Such a logical structure is not only more complex than the synchronous one, but it also introduces new risks and new families of errors (deadlocks, data-races...). Moreover, such less well designed, and more complex embedded software often utilizes more complex data-structures than synchronous programs (which typically only use arrays to store previous states) and may use dynamic memory allocation, or build dynamic structures inside static memory regions, which are actually even harder to verify than conventional dynamically allocated data structures. Complex data-structures also introduce new kinds of risks (the failure to maintain structural invariants may lead to runtime errors, non termination, or other software failures). To verify such programs, we will design additional abstract domains, and develop new static analysis techniques, in order to support the analysis of more complex programming language features such as parallel and concurrent programming with threads and manipulations of complex data structures. Due to their size and complexity, the verification of such families of embedded software is a major challenge for the research community.

Furthermore, embedded systems also give rise to novel security concerns. It is in particular the case for some aircraft-embedded computer systems, which communicate with the ground through untrusted communication media. Besides, the increasing demand for new capabilities, such as enhanced on-board connectivity, e.g. using mobile devices, together with the need for cost reduction, leads to more integrated and interconnected systems. For instance, modern aircrafts embed a large number of computer systems, from safety-critical cockpit avionics to passenger entertainment. Some systems meet both safety and security requirements.

Despite thorough segregation of subsystems and networks, some shared communication resources raise the concern of possible intrusions. Because of the size of such systems, and considering that they are evolving entities, the only economically viable alternative is to perform automatic analyses. Such analyses of security and confidentiality properties have never been achieved on large-scale systems where security properties interact with other software properties, and even the mapping between high-level models of the systems and the large software base implementing them has never been done and represents a great challenge. Our goal is to prove empirically that the security of such large scale systems can be proved formally, thanks to the design of dedicated abstract interpreters.

The long term goal is to make static analysis more widely applicable to the verification of industrial software.

4.2. Static analysis of software components and libraries

An important goal of our work is to make static analysis techniques easier to apply to wider families of software. Then, in the longer term, we hope to be able to verify less critical, yet very commonly used pieces of software. Those are typically harder to analyze than critical software, as their development process tends to be less rigorous. In particular, we will target operating systems components and libraries. As of today, the verification of such programs is considered a major challenge to the static analysis community.

As an example, most programming languages offer Application Programming Interfaces (API) providing ready-to-use abstract data structures (e.g., sets, maps, stacks, queues, etc.). These APIs, are known under the name of containers or collections, and provide off-the-shelf libraries of high level operations, such as insertion, deletion and membership checks. These container libraries give software developers a way of abstracting from low-level implementation details related to memory management, such as dynamic allocation, deletion and pointer handling or concurrency aspects, such as thread synchronization. Libraries implementing data structures are important building bricks of a huge number of applications, therefore their verification is paramount. We are interested in developing static analysis techniques that will prove automatically the correctness of large audience libraries such as Glib and Threading Building Blocks.

4.3. Models of mechanistic interactions between proteins

Computer Science takes a more and more important role in the design and the understanding of biological systems such as signaling pathways, self assembly systems, DNA repair mechanisms. Biology has gathered large data-bases of facts about mechanistic interactions between proteins, but struggles to draw an overall picture of how these systems work as a whole. High level languages designed in Computer Science allow one to collect these interactions in integrative models, and provide formal definitions (i.e., semantics) for the behavior of these models. This way, modelers can encode their knowledge, following a bottom-up discipline, without simplifying *a priori* the models at the risk of damaging the key properties of the system. Yet, the systems that are obtained this way suffer from combinatorial explosion (in particular, in the number of different kinds of molecular components, which can arise at run-time), which prevents from a naive computation of their behavior.

We develop various analyses based on abstract interpretation, and tailored to different phases of the modeling process. We propose automatic static analyses in order to detect inconsistencies in the early phases of the modeling process. These analyses are similar to the analysis of classical safety properties of programs. They involve both forward and backward reachability analyses as well as causality analyses, and can be tuned at different levels of abstraction. We also develop automatic static analyses in order to identify key elements in the dynamics of these models. The results of these analyses are sent to another tool, which is used to automatically simplify models. The correctness of this simplification process is proved by the means of abstract interpretation: this ensures formally that the simplification preserves the quantitative properties that have been specified beforehand by the modeler. The whole pipeline is parameterized by a large choice of abstract domains which exploits different features of the high level description of models.

4.4. Consensus

Fault-tolerant distributed systems provide a dependable service on top of unreliable computers and networks. Famous examples are geo-replicated data-bases, distributed file systems, or blockchains. Fault-tolerant protocols replicate the system and ensure that all (unreliable) replicas are perceived from the outside as one single reliable machine. To give the illusion of a single reliable machine “consensus” protocols force replicas to agree on the “current state” before making this state visible to an outside observer. We are interested in (semi-)automatically proving the total correctness of consensus algorithms in the benign case (messages are lost or processes crash) or the Byzantine case (processes may lie about their current state). In order to do this, we first define new reduction theorems to simplify the behaviors of the system and, second, we introduce new static analysis methods to prove the total correctness of adequately simplified systems. We focus on static analysis based Satisfiability Modulo Theories (SMT) solvers which offers a good compromise between automation and expressiveness. Among our benchmarks are Paxos, PBFT (Practical Byzantine Fault-Tolerance), and blockchain algorithms (Red-Belly, Tendermint, Algorand). These are highly challenging benchmarks, with a lot of non-determinism coming from the interleaving semantics and from the adversarial environment in which correct processes execute, environment that can drop messages, corrupt them, etc. Moreover, these systems were originally designed for a few servers but today are deployed on networks with thousands of nodes. The “optimizations” for scalability can no longer be overlooked and must be considered as integral part of the algorithms, potentially leading to specifications weaker than the so much desired consensus.

4.5. Models of growth

In systems and synthetic biology (engineered systems) one would like study the environment of a given cellular process (such as signaling pathways mentioned earlier) and the ways in which that process interacts with different resources provided by the host. To do this, we have built coarse-grained models of cellular physiology which summarize fundamental processes (transcription, translation, transport, metabolism). such models describe global growth in mechanistic way and allow one to plug the model of one’s process of interest into a simplified and yet realistic and reactive model of the process interaction with its immediate environment. A first ODE-based deterministic version of this model [26] explaining the famous bacterial growth laws and how the allocation of resources to different genomic sectors depends on the growth conditions- was published in 2015 and has already received nearly 150 citations. The model also allows one to bridge between population genetic models which describe cells in terms of abstract features and fitness and intra-cellular models. For instance, we find that fastest growing strategies are not evolutionary stable in competitive experiments. We also find that vastly different energy storage strategies exist [24]. In a recent article [25] in *Nature Communications* we build a stochastic version of the above model. We predict the empirical size and doubling time distributions as a function of growth conditions. To be able to fit the parameters of the model to available single-cell data (note that the fitting constraints are far tighter than in the deterministic case), we introduce new techniques for the approximation of reaction-division systems which generalize continuous approximations of Langevin type commonly used for pure reaction systems. We also use cross-correlations to visualize causality and modes in noise propagation in the model (in a way reminiscent to abstract computational traces mentioned earlier). In other work, we show how to connect our new class of models to more traditional ones stemming from “flux balance analysis” by introducing an allocation vector which allows one to assign a formal growth rate to a class of reaction systems [20].

4.6. Static analysis of data science software

Nowadays, thanks to advances in machine learning and the availability of vast amounts of data, computer software plays an increasingly important role in assisting or even autonomously performing tasks in our daily lives. As data science software becomes more and more widespread, we become increasingly vulnerable to programming errors. In particular, programming errors that do not cause failures can have serious consequences since code that produces an erroneous but plausible result gives no indication that something went wrong. This issue becomes particularly worrying knowing that machine learning software, thanks to its ability

to efficiently approximate or simulate more complex systems, is slowly creeping into mission critical scenarios. However, programming errors are not the only concern. Another important issue is the vulnerability of machine learning models to adversarial examples, that is, small input perturbations that cause the model to misbehave in unpredictable ways. More generally, a critical issue is the notorious difficulty to interpret and explain machine learning software. Finally, as we are witnessing widespread adoption of software with far-reaching societal impact — i.e., to automate decision-making in fields such as social welfare, criminal justice, and even health care — a number of recent cases have evidenced the importance of ensuring software fairness as well as data privacy. Going forward, data science software will be subject to more and more legal regulations (e.g., the European General Data Protection Regulation adopted in 2016) as well as administrative audits. It is thus paramount to develop method and tools that can keep up with these developments and enhance our understanding of data science software and ensure it behaves correctly and reliably. In particular, we are interesting in developing new static analyses specifically tailored to the idiosyncrasies of data science software. This makes it a new and exciting area for static analysis, offering a wide variety of challenging problems with huge potential impact on various interdisciplinary application domains [13].

CAMBIUM Project-Team

4. Application Domains

4.1. Formal methods

We develop techniques and tools for the formal verification of critical software:

- program logics based on CFML and Iris for the deductive verification of software, including concurrency and algorithmic complexity aspects;
- verified development tools such as the CompCert verified C compiler, which extends properties established by formal verification at the source level all the way to the final executable code.

Some of these techniques have already been used in the nuclear industry (MTU Friedrichshafen uses CompCert to develop emergency diesel generators) and are under evaluation in the aerospace industry.

4.2. High-assurance software

Software that is not critical enough to undergo formal verification can still benefit greatly, in terms of reliability and security, from a functional, statically-typed programming language. The OCaml type system offers several advanced tools (generalized algebraic data types, abstract types, extensible variant and object types) to express many data structure invariants and safety properties and have them automatically enforced by the type-checker. This makes OCaml a popular language to develop high-assurance software, in particular in the financial industry. OCaml is the implementation language for the Tezos blockchain and cryptocurrency. It is also used for automated trading at Jane Street and for modeling and pricing of financial contracts at Bloomberg, Lexifi and Simcorp. OCaml is also widely used to implement code verification and generation tools at Facebook, Microsoft, CEA, Esterel Technologies, and many academic research groups, at Inria and elsewhere.

4.3. Design and test of microprocessors

The **diy** tool suite and the underlying methodology is in use at ARM Ltd to design and test the memory model of ARM architectures. In particular, the internal reference memory model of the ARMv8 (or AArch64) architecture has been written “in house” in Cat, our domain-specific language for specifying and simulating memory models. Moreover, our test generators and runtime infrastructure are used routinely at ARM to test various implementations of their architectures.

4.4. Teaching programming

Our work on the OCaml language family has an impact on the teaching of programming. OCaml is one of the programming languages selected by the French Ministry of Education for teaching Computer Science in classes préparatoires scientifiques. OCaml is also widely used for teaching advanced programming in engineering schools, colleges and universities in France, the USA, and Japan. The MOOC “Introduction to Functional Programming in OCaml”, developed at University Paris Diderot, is available on the France Université Numérique platform and comes with an extensive platform for self-training and automatic grading of exercises, developed in OCaml itself.

CASCADE Project-Team

4. Application Domains

4.1. Privacy for the Cloud

Many companies have already started the migration to the Cloud and many individuals share their personal informations on social networks. While some of the data are public information, many of them are personal and even quite sensitive. Unfortunately, the current access mode is purely right-based: the provider first authenticates the client, and grants him access, or not, according to his rights in the access-control list. Therefore, the provider itself not only has total access to the data, but also knows which data are accessed, by whom, and how: privacy, which includes secrecy of data (confidentiality), identities (anonymity), and requests (obliviousness), should be enforced. Moreover, while high availability can easily be controlled, and thus any defect can immediately be detected, failures in privacy protection can remain hidden for a long time. The industry of the Cloud introduces a new implicit trust requirement: nobody has any idea at all of where and how his data are stored and manipulated, but everybody should blindly trust the providers. The providers will definitely do their best, but this is not enough. Privacy-compliant procedures cannot be left to the responsibility of the provider: however strong the trustfulness of the provider may be, any system or human vulnerability can be exploited against privacy. This presents too huge a threat to tolerate. *The distribution of the data and the secrecy of the actions must be given back to the users. It requires promoting privacy as a global security notion.*

In order to protect the data, one needs to encrypt it. Unfortunately, traditional encryption systems are inadequate for most applications involving big, complex data. Recall that in traditional public key encryption, a party encrypts data to a single known user, which lacks the expressiveness needed for more advanced data sharing. In enterprise settings, a party will want to share data with groups of users based on their credentials. Similarly, individuals want to selectively grant access to their personal data on social networks as well as documents and spreadsheets on Google Docs. Moreover, the access policy may even refer to users who do not exist in the system at the time the data is encrypted. Solving this problem requires an entirely new way of encrypting data.

A first natural approach would be **fully homomorphic encryption** (FHE, see above), but a second one is also **functional encryption**, that is an emerging paradigm for public-key encryption: it enables more fine-grained access control to encrypted data, for instance, the ability to specify a decryption policy in the ciphertext so that only individuals who satisfy the policy can decrypt, or the ability to associate keywords to a secret key so that it can only decrypt documents containing the keyword. Our work on functional encryption centers around two goals:

1. to obtain more efficient pairings-based functional encryption;
2. and to realize new functionalities and more expressive functional encryption schemes.

Another approach is **secure multi-party computation protocols**, where interactivity might provide privacy in a more efficient way. Recent implicit interactive proofs of knowledge can be a starting point. But stronger properties are first expected for improving privacy. They can also be integrated into new ad-hoc broadcast systems, in order to distribute the management among several parties, and eventually remove any trust requirements.

Strong privacy for the Cloud would have a huge societal impact since it would revolutionize the trust model: users would be able to make safe use of outsourced storage, namely for personal, financial and medical data, without having to worry about failures or attacks of the server.

KOPERNIC Team

4. Application Domains

4.1. Avionics

This work is based on a direct collaboration between Airbus and Inria, complementary to collaborative projects like PIA LEOC Capacites and CIFRE thesis. The time critical solutions in this context are based on temporal and spatial isolation of the programs and the understanding of multicore interferences is crucial. Our contributions belong mainly to the solutions space for the objective identified in Section 3.1 .

4.2. Railway

This work is based on a direct collaboration with Clearsy and SNCF, complementary to collaborative projects like PIA BGLE Departs and FUI 21 Waruna. The time critical solutions in this context concern both the proposition of an appropriate scheduler and associated schedulability analyses. Our contributions belong to the solutions space of problems dealt within the objectives identified in Section 3.1 .

4.3. Autonomous cars

This work is based on a direct collaboration with RITS (Inria project team). The time critical solutions in this context concern the interaction between programs executed on multicore processors and messages transmitted through wireless communication channels. Our contributions belong to the solutions space of all three classes of problems dealt within the objectives identified in Section 3.2 .

4.4. Drones

This work is based on the collaborative project FUI/FEDER 22 Ceos. As in the case of autonomous cars, there is an interaction between programs and messages, suggesting that our contributions in this context belong to the solutions space of all three classes of problems dealt within the objectives identified in Section 3.2 .

OURAGAN Project-Team

4. Application Domains

4.1. Security of cryptographic systems

The study of the security of asymmetric cryptographic systems comes as an application of the work carried out in algorithmic number theory and revolves around the development and the use of a small number of general purpose algorithms (lattice reduction, class groups in number fields, discrete logarithms in finite fields, ...). For example, the computation of generators of principal ideals of cyclotomic fields can be seen as one of these applications since these are used in a number of recent public key cryptosystems.

The cryptographic community is currently very actively assessing the threat coming for the development of quantum computers. Indeed, such computers would permit tremendous progress on many number theoretic problems such as factoring or discrete logarithm computations and would put the security of current cryptosystem under a major risk. For this reason, there is a large global research effort dedicated to finding alternative methods of securing data. For example, the US standardization agency called NIST has recently launched a standardization process around this issue. In this context, OURAGAN is part of the competition and has submitted a candidate (which has not been selected) [40]. This method is based on number-theoretic ideas involving a new presumably difficult problem concerning the Hamming distance of integers modulo large numbers of Mersenne.

4.2. Robotics

Algebraic computations have tremendously been used in Robotics, especially in kinematics, since the last quarter of the 20th century [93]. For example, one can find algebraic proofs for the 40 possible solutions to the direct kinematics problem [117] for Stewart platforms and companion experiments based on Gröbner basis computations [83]. On the one hand, hard general kinematics problems involve too many variables for pure algebraic methods to be used in place of existing numerical or semi-numerical methods everywhere and everytime, and on the other hand, global algebraic studies allow to propose exhaustive classifications that cannot be reached by other methods, for some quite large classes.

Robotics is a long-standing collaborative work with LS2N (Laboratory of Numerical Sciences of Nantes). Work has recently focused on the offline study of mechanisms, mostly parallel, their singularities or at least some types of singularities (cuspidal robots [140]).

For most parallel or serial manipulators, pose variables and joints variables are linked by algebraic equations and thus lie on an algebraic variety. The two-kinematics problems (the direct kinematics problem - DKP- and the inverse kinematics problem - IKP) consist in studying the preimage of the projection of this algebraic variety onto a subset of unknowns. Solving the DKP remains to computing the possible positions for a given set of joint variables values while solving the IKP remains to computing the possible joints variables values for a given position. Algebraic methods have been deeply used in several situations for studying parallel and serial mechanisms, but finally their use stays quite confidential in the design process. Cylindrical Algebraic Decomposition coupled with variable's eliminations by means of Gröbner based computations can be used to model the workspace, the joint space and the computation of singularities. On the one hand, such methods suffer immediately when increasing the number of parameters or when working with imprecise data. On the other hand, when the problem can be handled, they might provide full and exhaustive classifications. The tools we use in that context [60], [59], [95], [97], [96] depend mainly on the resolution of parameter-based systems and therefore of study-dependent curves or flat algebraic surfaces (2 or 3 parameters), thus joining our thematic *Computational Geometry*.

4.3. Control theory

Certain problems studied in mathematical systems theory and control theory can be better understood and finely studied by means of algebraic structures and methods. Hence, the rich interplay between algebra, computer algebra, and control theory has a long history. For instance, the first main paper on Gröbner bases written by their creators, Buchberger, was published in Bose's book [46] on control theory of multidimensional systems. Moreover, the differential algebra approach to nonlinear control theory (see [72], [73] and the references therein) was a major motivation for the algorithmic study of differential algebra [47], [76]. Finally, the behaviour approach to linear systems theory [141], [119] advocates for an algorithmic study of algebraic analysis (see Section 2.2.4). More generally, control theory is porous to computer algebra since one finds algebraic criteria of all kinds in the literature even if the control theory community has a very few knowledge in computer algebra.

OURAGAN has a strong interest in the computer algebra aspects of mathematical systems theory and control theory related to both functional and polynomial systems, particularly in the direction of robust stability analysis and robust stabilization problems for multidimensional systems [46], [119] and infinite-dimensional systems [66] (such as, e.g., differential time-delay systems).

Let us shortly state a few points of our recent interests in this direction.

In control theory, stability analysis of linear time-invariant control systems is based on the famous Routh-Hurwitz criterion (late 19th century) and its relation with Sturm sequences and Cauchy index. Thus, stability tests were only involving tools for univariate polynomials [102]. While extending those tests to multidimensional systems or differential time-delay systems, one had to tackle multivariate problems recursively with respect to the variables [46]. Recent works use a mix of symbolic/numeric strategies, Linear Matrix Inequalities (LMI), sums of squares, etc. But still very few practical experiments are currently involving certified algebraic computations based on general solvers for polynomial equations. We have recently started to study certified stability tests for multidimensional systems or differential time-delay systems with an important observation: with a correct modelization, some recent algebraic methods – derived from our work in algorithmic geometry and shared with applications in robotics – can now handle previously impossible computations and lead to a better understanding of the problems to be solved [52], [54], [55]. The previous approaches seem to be blocked on a recursive use of one-variable methods, whereas our approach involves the direct processing of the problem for a larger number of variables.

The structural stability of n -D discrete linear systems (with $n \geq 2$) is a good source of problems of several kinds ranging from solving univariate polynomials to studying algebraic systems depending on parameters. For instance, we show [53], [54], [55] that the standard characterization of the structural stability of a multivariate rational transfer function (namely, the denominator of the transfer function does not have solutions in the unit polydisc of \mathbb{C}^n) is equivalent to deciding whether or not a certain system of polynomial equations has real solutions. The use state-of-the-art computer algebra algorithms to check this last condition, and thus the structural stability of multidimensional systems has been validated in several situations from toy examples with parameters to state-of-the-art examples involving, e.g., the resolution of bivariate systems [51], [50].

The rich interplay between control theory, algebra, and computer algebra is also well illustrated with our recent work on robust stabilization problems for multidimensional and finite/infinite-dimensional systems [48], [123], [129], [132], [130], [131].

4.4. Signal processing

Due to numerous applications (e.g. sensor network, mobile robots), sources and sensors localization has intensively been studied in the literature of signal processing. The *anchor position self calibration problem* is a well-known problem which consists in estimating the positions of both the moving sources and a set of fixed sensors (anchors) when only the distance information between the points from the different sets is available. The position self-calibration problem is a particular case of the *Multidimensional Unfolding* (MDU) problem for the Euclidean space of dimension 3. In the signal processing literature, this problem is attacked by means of optimization problems (see [65] and the references therein). Based on computer algebra methods for

polynomial systems, we have recently developed a new approach for the MDU problem which yields closed-form solutions and a very efficient algorithm for the estimation of the positions [68] based only on linear algebra techniques. This first result, done in collaboration with Dagher (Inria Chile) and Zheng (DEFROST, Inria Lille), yielded a recent patent [67]. This result advocates for the study of other localization problems based on the computational polynomial techniques developed in OURAGAN.

In collaboration with *Safran Tech* (Barau, Hubert) and Dagher (Inria Chile), a symbolic-numeric study of the new *multi-carrier demodulation method* [92] has recently been initiated. *Gear fault diagnosis* is an important issue in aeronautics industry since a damage in a gearbox, which is not detected in time, can have dramatic effects on the safety of a plane. Since the vibrations of a spur gear can be modeled as a product of two periodic functions related to the gearbox kinematic, it is proposed to recover each function from the global signal by means of an optimal reconstruction problem which, based on Fourier analysis, can be rewritten as $\operatorname{argmin}_{u \in \mathbb{C}^n, v_1, v_2 \in \mathbb{C}^m} \|M - u v_1^{\star} - D u v_2^{\star}\|_F$, where $M \in \mathbb{C}^{n \times m}$ (resp. $D \in \mathbb{C}^{n \times n}$) is a given matrix with a special shape (resp. diagonal matrix), $\|\cdot\|_F$ is the Frobenius norm, and v^{\star} is the Hermitian transpose of v . We have recently obtained closed-form solutions for the exact problem, i.e., $M = u v_1^{\star} + D u v_2^{\star}$, which is a polynomial system with parameters. This first result gives interesting new insides for the study of the non-exact case, i.e. for the above optimization problem.

Our expertise on *algebraic parameter estimation problem*, developed in the former NON-A project-team (Inria Lille), will be further developed. Following this work [84], the problem consists in estimating a set θ of parameters of a signal $x(\theta, t)$ — which satisfies a certain dynamics — when the signal $y(t) = x(\theta, t) + \gamma(t) + \varpi(t)$ is observed, where γ denotes a structured perturbation and ϖ a noise. It has been shown that θ can sometimes be explicitly determined by means of closed-form expressions using iterated integrals of y . These integrals are used to filter the noise ϖ . Based on a combination of algebraic analysis techniques (rings of differential operators), differential elimination theory (Gröbner basis techniques for Weyl algebras), and operational calculus (Laplace transform, convolution), an algorithmic approach to algebraic parameter estimation problem has been initiated in [125] for a particular type of structured perturbations (i.e. bias) and was implemented in the Maple prototype NonA. The case of a general structured perturbation is still lacking.

PARKAS Project-Team

4. Application Domains

4.1. Embedded Control Software

Embedded control software defines the interactions of specialized hardware with the physical world. It normally ticks away unnoticed inside systems like medical devices, trains, aircraft, satellites, and factories. This software is complex and great effort is required to avoid potentially serious errors, especially over many years of maintenance and reuse.

Engineers have long designed such systems using block diagrams and state machines to represent the underlying mathematical models. One of the key insights behind synchronous programming languages is that these models can be executable and serve as the base for simulation, validation, and automatic code generation. This approach is sometimes termed Model-Based Development (MBD). The SCADE language and associated code generator allow the application of MBD in safety-critical applications. They incorporate ideas from LUSTRE, LUCID SYNCHRONE, and other programming languages.

4.2. Hybrid Systems Design and Simulation

Modern embedded systems are increasingly conceived as rich amalgams of software, hardware, networking, and physical processes. The terms Cyberphysical System (CPS) or Internet-of-Things (IoT) are sometimes used as labels for this point of view.

In terms of modeling languages, the main challenges are to specify both discrete and continuous processes in a single *hybrid* language, give meaning to their compositions, simulate their interactions, analyze the behavior of the overall system, and extract code either for target control software or more efficient, possibly online, simulation. Languages like Simulink and Modelica are already used in the design and analysis of embedded systems; it is more important than ever to understand their underlying principles and to propose new constructs and analyses.

PI.R2 Project-Team (section vide)

POLSYS Project-Team (section vide)

PROSECCO Project-Team

4. Application Domains

4.1. Cryptographic Protocol Libraries

Cryptographic protocols such as TLS, SSH, IPsec, and Kerberos are the trusted base on which the security of modern distributed systems is built. Our work enables the analysis and verification of such protocols, both in their design and implementation. Hence, for example, we build and verify models and reference implementations for well-known protocols such as TLS and SSH, as well as analyze their popular implementations such as OpenSSL.

4.2. Hardware-based security APIs

Cryptographic devices such as Hardware Security Modules (HSMs) and smartcards are used to protect long-term secrets in tamper-proof hardware, so that even attackers who gain physical access to the device cannot obtain its secrets. These devices are used in a variety of scenarios ranging from bank servers to transportation cards (e.g. Navigo). Our work investigates the security of commercial cryptographic hardware and evaluates the APIs they seek to implement.

4.3. Web application security

Web applications use a variety of cryptographic techniques to securely store and exchange sensitive data for their users. For example, a website may serve pages over HTTPS, authenticate users with a single sign-on protocol such as OAuth, encrypt user files on the server-side using XML encryption, and deploy client-side cryptographic mechanisms using a JavaScript cryptographic library. The security of these applications depends on the public key infrastructure (X.509 certificates), web browsers' implementation of HTTPS and the same origin policy (SOP), the semantics of JavaScript, HTML5, and their various associated security standards, as well as the correctness of the specific web application code of interest. We build analysis tools to find bugs in all these artifacts and verification tools that can analyze commercial web applications and evaluate their security against sophisticated web-based attacks.

SECRET Project-Team

4. Application Domains

4.1. Cryptographic primitives

Our major application domain is the design of cryptographic primitives, especially for platforms with restricting implementation requirements. For instance, we aim at recommending (or designing) low-cost (or extremely fast) encryption schemes, or primitives which remain secure against quantum computers.

4.2. Code Reconstruction

To evaluate the quality of a cryptographic algorithm, it is usually assumed that its specifications are public, as, in accordance with Kerckhoffs principle, it would be dangerous to rely, even partially, on the fact that the adversary does not know those specifications. However, this fundamental rule does not mean that the specifications are known to the attacker. In practice, before mounting a cryptanalysis, it is necessary to strip off the data. This reverse-engineering process is often subtle, even when the data formatting is not concealed on purpose. A typical case is interception: some raw data, not necessarily encrypted, is observed out of a noisy channel. To access the information, the whole communication system has first to be disassembled and every constituent reconstructed. A transmission system actually corresponds to a succession of elements (symbol mapping, scrambler, channel encoder, interleaver...), and there exist many possibilities for each of them. In addition to the “preliminary to cryptanalysis” aspect, there are other links between those problems and cryptology. They share some scientific tools (algorithmics, discrete mathematics, probability...), but beyond that, there are some very strong similarities in the techniques.

CAGE Project-Team

4. Application Domains

4.1. First axis: Geometry of vision

A suggestive application of sub-Riemannian geometry and in particular of hypoelliptic diffusion comes from a model of geometry of vision describing the functional architecture of the primary visual cortex V1. In 1958, Hubel and Wiesel (Nobel in 1981) observed that the visual cortex V1 is endowed with the so-called **pinwheel structure**, characterized by neurons grouped into orientation columns, that are sensible both to positions and directions [110]. The mathematical rephrasing of this discovery is that the visual cortex lifts an image from \mathbf{R}^2 into the bundle of directions of the plane [97], [136], [138], [109].

A simplified version of the model can be described as follows: neurons of V1 are grouped into orientation columns, each of them being sensitive to visual stimuli at a given point of the retina and for a given direction on it. The retina is modeled by the real plane, i.e., each point is represented by a pair $(x, y) \in \mathbf{R}^2$, while the directions at a given point are modeled by the projective line, i.e. an element θ of the projective line P^1 . Hence, the primary visual cortex V1 is modeled by the so called projective tangent bundle $\text{PTR}^2 = \mathbf{R}^2 \times \mathbf{P}^1$. From a neurological point of view, orientation columns are in turn grouped into hypercolumns, each of them being sensitive to stimuli at a given point (x, y) with any direction.

Orientation columns are connected between them in two different ways. The first kind of connections are the vertical (inhibitory) ones, which connect orientation columns belonging to the same hypercolumn and sensible to similar directions. The second kind of connections are the horizontal (excitatory) connections, which connect neurons belonging to different (but not too far) hypercolumns and sensible to the same directions. The resulting metric structure is sub-Riemannian and the model obtained in this way provides a convincing explanation in terms of sub-Riemannian geodesics of gestalt phenomena such as Kanizsa illusory contours.

The sub-Riemannian model for image representation of V1 has a great potential of yielding powerful bio-inspired image processing algorithms [104], [90]. Image inpainting, for instance, can be implemented by reconstructing an incomplete image by activating orientation columns in the missing regions in accordance with sub-Riemannian non-isotropic constraints. The process intrinsically defines an hypoelliptic heat equation on PTR^2 which can be integrated numerically using non-commutative Fourier analysis on a suitable semidiscretization of the group of roto-translations of the plane [88].

We have been working on the model and its software implementation since 2012. This work has been supported by several project, as the ERC starting grant GeCoMethods and the ERC Proof of Concept ARTIV1 of U. Boscain, and the ANR GCM.

A parallel approach that we will pursue and combine with this first one is based on **pattern matching in the group of diffeomorphisms**. We want to extend this approach, already explored in the Riemannian setting [151], [127], to the general sub-Riemannian framework. The paradigm of the approach is the following: consider a distortable object, more or less rigid, discretized into a certain number of points. One may track its distortion by considering the paths drawn by these points. One would however like to know how the object itself (and not its discretized version) has been distorted. The study in [151], [127] shed light on the importance of Riemannian geometry in this kind of problem. In particular, they study the Riemannian submersion obtained by making the group of diffeomorphisms act transitively on the manifold formed by the points of the discretization, minimizing a certain energy so as to take into account the whole object. Settled as such, the problem is Riemannian, but if one considers objects involving connections, or submitted to nonholonomic constraints, like in medical imaging where one tracks the motions of organs, then one comes up with a sub-Riemannian problem. The transitive group is then far bigger, and the aim is to lift curves submitted to these nonholonomic constraints into curves in the set of diffeomorphisms satisfying the corresponding constraints, in a unique way and minimizing an energy (giving rise to a sub-Riemannian structure).

4.2. Second axis: Quantum control

The goal of quantum control is to design efficient protocols for tuning the occupation probabilities of the energy levels of a system. This task is crucial in atomic and molecular physics, with applications ranging from photochemistry to nuclear magnetic resonance and quantum computing. A quantum system may be controlled by exciting it with one or several external fields, such as magnetic or electric fields. The goal of quantum control theory is to adapt the tools originally developed by control theory and to develop new specific strategies that tackle and exploit the features of quantum dynamics (probabilistic nature of wavefunctions and density operators, measure and wavefunction collapse, decoherence, ...). A rich variety of relevant models for controlled quantum dynamics exist, encompassing low-dimensional models (e.g., single-spin systems) and PDEs alike, with deterministic and stochastic components, making it a rich and exciting area of research in control theory.

The controllability of quantum system is a well-established topic when the state space is finite-dimensional [102], thanks to general controllability methods for left-invariant control systems on compact Lie groups [92], [112]. When the state space is infinite-dimensional, it is known that in general the bilinear Schrödinger equation is not exactly controllable [154]. Nevertheless, weaker controllability properties, such as approximate controllability or controllability between eigenstates of the internal Hamiltonian (which are the most relevant physical states), may hold. In certain cases, when the state space is a function space on a 1D manifold, some rather precise description of the set of reachable states has been provided [77]. A similar description for higher-dimensional manifolds seems intractable and at the moment only approximate controllability results are available [128], [134], [113]. The most widely applicable tests for controllability of quantum systems in infinite-dimensional Hilbert spaces are based on the **Lie–Galerkin technique** [96], [85], [86]. They allow, in particular, to show that the controllability property is generic among this class of systems [125].

A family of algorithms which are specific to quantum systems are those based on adiabatic evolution [158], [157], [116]. The basic principle of adiabatic control is that the flow of a slowly varying Hamiltonian can be approximated (up to a phase factor) by a quasi-static evolution, with a precision proportional to the velocity of variation of the Hamiltonian. The advantage of the **adiabatic approach** is that it is constructive and produces control laws which are both smooth and robust to parameter uncertainty. The paradigm is based on the adiabatic perturbation theory developed in mathematical physics [83], [133], [150], where it plays an important role for understanding molecular dynamics. Approximation theory by adiabatic perturbation can be used to describe the evolution of the occupation probabilities of the energy levels of a slowly varying Hamiltonian. Results from the last 15 years, including those by members of our team [64], [89], have highlighted the effectiveness of control techniques based on adiabatic path following.

4.3. Third axis: Stability and uncertain dynamics

Switched and hybrid systems constitute a broad framework for the description of the heterogeneous aspects of systems in which continuous dynamics (typically pertaining to physical quantities) interact with discrete/logical components. The development of the switched and hybrid paradigm has been motivated by a broad range of applications, including automotive and transportation industry [142], energy management [135] and congestion control [126].

Even if both controllability [146] and observability [114] of switched and hybrid systems have attracted much research efforts, the central role in their study is played by the problem of stability and stabilizability. The goal is to determine whether a dynamical or a control system whose evolution is influenced by a time-dependent signal is uniformly stable or can be uniformly stabilized [119], [147]. Uniformity is considered with respect to all signals in a given class. Stability of switched systems lead to several interesting phenomena. For example, even when all the subsystems corresponding to a constant switching law are exponentially stable, the switched systems may have divergent trajectories for certain switching signals [118]. This fact illustrates the fact that stability of switched systems depends not only on the dynamics of each subsystem but also on the properties of the class of switching signals which is considered.

The most common class of switching signals which has been considered in the literature is made of all piecewise constant signals. In this case uniform stability of the system is equivalent to the existence of a common quadratic Lyapunov function [129]. Moreover, provided that the system has finitely many modes, the Lyapunov function can be taken polyhedral or polynomial [80], [81], [103]. A special role in the switched control literature has been played by common quadratic Lyapunov functions, since their existence can be tested rather efficiently (see the surveys [121], [141] and the references therein). It is known, however, that the existence of a common quadratic Lyapunov function is not necessary for the global uniform exponential stability of a linear switched system with finitely many modes. Moreover, there exists no uniform upper bound on the minimal degree of a common polynomial Lyapunov function [124]. More refined tools rely on multiple and non-monotone Lyapunov functions [91]. Let us also mention linear switched systems technics based on the analysis of the Lie algebra generated by the matrices corresponding to the modes of the system [67].

For systems evolving in the plane, more geometrical tests apply, and yield a complete characterization of the stability [84], [73]. Such a geometric approach also yields sufficient conditions for uniform stability in the linear planar case [87].

In many situations, it is interesting for modeling purposes to specify the features of the switched system by introducing **constrained switching rules**. A typical constraint is that each mode is activated for at least a fixed minimal amount of time, called the dwell-time. Switching rules can also be imposed, for instance, by a timed automata. When constraints apply, the common Lyapunov function approach becomes conservative and new tools have to be developed to give more detailed characterizations of stable and unstable systems.

Our approach to constrained switching is based on the idea of relating the analytical properties of the classes of constrained switching laws (shift-invariance, compactness, closure under concatenation, ...) to the stability behavior of the corresponding switched systems. One can introduce **probabilistic uncertainties** by endowing the classes of admissible signals with suitable probability measures. One then looks at the corresponding Lyapunov exponents, whose existence is established by the multiplicative ergodic theorem. The interest of this approach is that probabilistic stability analysis filters out highly ‘exceptional’ worst-case trajectories. Although less explicitly characterized from a dynamical viewpoint than its deterministic counterpart, the probabilistic notion of uniform exponential stability can be studied using several reformulations of Lyapunov exponents proposed in the literature [78], [98], [155].

4.4. Joint theoretical core

The theoretical questions raised by the different applicative area will be pooled in a research axis on the transversal aspects of geometric control theory and sub-Riemannian structures.

We recall that sub-Riemannian geometry is a generalization of Riemannian geometry, whose birth dates back to Carathéodory’s seminal paper on the foundations of Carnot thermodynamics [94], followed by E. Cartan’s address at the International Congress of Mathematicians in Bologna [95]. In the last twenty years, sub-Riemannian geometry has emerged as an independent research domain, with a variety of motivations and ramifications in several parts of pure and applied mathematics. Let us mention geometric analysis, geometric measure theory, stochastic calculus and evolution equations together with applications in mechanics and optimal control (motion planning, robotics, nonholonomic mechanics, quantum control) [62], [63].

One of the main open problems in sub-Riemannian geometry concerns the regularity of length-minimizers [65], [131]. Length-minimizers are solutions to a variational problem with constraints and satisfy a first-order necessary condition resulting from the Pontryagin Maximum Principle (PMP). Solutions of the PMP are either *normal* or *abnormal*. Normal length-minimizers are well-known to be smooth, i.e., C^∞ , as it follows by the Hamiltonian nature of the PMP. The question of regularity is then reduced to abnormal length-minimizers. If the sub-Riemannian structure has step 2, then abnormal length-minimizers can be excluded and thus every length-minimizer is smooth. For step 3 structures, the situation is already more complicated and smoothness of length-minimizers is known only for Carnot groups [115], [149]. The question of regularity of length-minimizers is not restricted to the smoothness in the C^∞ sense. A recent result prove that length-minimizers, for sub-Riemannian structures of any step, cannot have corner-like singularities [108]. When the

sub-Riemannian structure is analytic, more is known on the size of the set of points where a length-minimizer can lose analyticity [148], regardless of the rank and of the step of the distribution.

An interesting set of recent results in sub-Riemannian geometry concerns the extension to such a setting of the Riemannian notion of sectional curvature. The curvature operator can be introduced in terms of the symplectic invariants of the Jacobi curve [69], [117], [66], a curve in the Lagrange Grassmannian related to the linearization of the Hamiltonian flow. Alternative approaches to curvatures in metric spaces are based either on the associated heat equation and the generalization of the curvature-dimension inequality [74], [75] or on optimal transport and the generalization of Ricci curvature [145], [144], [123], [71].

MATERIALS Project-Team (section vide)

MATHRISK Project-Team

4. Application Domains

4.1. Financial Mathematics, Insurance

The domains of application are quantitative finance and insurance with emphasis on risk modeling and control. In particular, Mathrisk focuses on dependence modeling, systemic risk, market microstructure modeling and risk measures.

MOKAPLAN Project-Team (section vide)

QUANTIC Project-Team

4. Application Domains

4.1. Quantum engineering

A new field of quantum systems engineering has emerged during the last few decades. This field englobes a wide range of applications including nano-electromechanical devices, nuclear magnetic resonance applications, quantum chemical synthesis, high resolution measurement devices and finally quantum information processing devices for implementing quantum computation and quantum communication. Recent theoretical and experimental achievements have shown that the quantum dynamics can be studied within the framework of estimation and control theory, but give rise to new models that have not been fully explored yet.

The QUANTIC team's activities are defined at the border between theoretical and experimental efforts of this emerging field with an emphasis on the applications in quantum information, computation and communication. The main objective of this interdisciplinary team is to develop quantum devices ensuring a robust processing of quantum information.

On the theory side, this is done by following a system theory approach: we develop estimation and control tools adapted to particular features of quantum systems. The most important features, requiring the development of new engineering methods, are related to the concept of measurement and feedback for composite quantum systems. The destructive and partial⁰ nature of measurements for quantum systems lead to major difficulties in extending classical control theory tools. Indeed, design of appropriate measurement protocols and, in the sequel, the corresponding quantum filters estimating the state of the system from the partial measurement record, are themselves building blocks of the quantum system theory to be developed.

On the experimental side, we develop new quantum information processing devices based on quantum superconducting circuits. Indeed, by realizing superconducting circuits at low temperatures and using microwave measurement techniques, the macroscopic and collective degrees of freedom such as the voltage and the current are forced to behave according to the laws of quantum mechanics. Our quantum devices are aimed to protect and process quantum information through these integrated circuits.

⁰Here the partiality means that no single quantum measurement is capable of providing the complete information on the state of the system.

SIERRA Project-Team

4. Application Domains

4.1. Applications for Machine Learning

Machine learning research can be conducted from two main perspectives: the first one, which has been dominant in the last 30 years, is to design learning algorithms and theories which are as generic as possible, the goal being to make as few assumptions as possible regarding the problems to be solved and to let data speak for themselves. This has led to many interesting methodological developments and successful applications. However, we believe that this strategy has reached its limit for many application domains, such as computer vision, bioinformatics, neuro-imaging, text and audio processing, which leads to the second perspective our team is built on: Research in machine learning theory and algorithms should be driven by interdisciplinary collaborations, so that specific prior knowledge may be properly introduced into the learning process, in particular with the following fields:

- Computer vision: object recognition, object detection, image segmentation, image/video processing, computational photography. In collaboration with the Willow project-team.
- Bioinformatics: cancer diagnosis, protein function prediction, virtual screening. In collaboration with Institut Curie.
- Text processing: document collection modeling, language models.
- Audio processing: source separation, speech/music processing.
- Neuro-imaging: brain-computer interface (fMRI, EEG, MEG).

ANGE Project-Team

4. Application Domains

4.1. Overview

Sustainable development and environment preservation have a growing importance and scientists have to address difficult issues such as: management of water resources, renewable energy production, bio/geo-chemistry of oceans, resilience of society w.r.t. hazardous flows, urban pollutions, ...

As mentioned above, the main issue is to propose models of reduced complexity, suitable for scientific computing and endowed with stability properties (continuous and/or discrete). In addition, models and their numerical approximations have to be confronted with experimental data, as analytical solutions are hardly accessible for these problems/models. A. Mangeney (IPGP) and N. Goutal (EDF) may provide useful data.

4.2. Geophysical flows

Reduced models like the shallow water equations are particularly well-adapted to the modelling of geophysical flows since they are characterized by large time or/and space scales. For long time simulations, the preservation of equilibria is essential as global solutions are a perturbation around them. The analysis and the numerical preservation of non-trivial equilibria, more precisely when the velocity does not vanish, are still a challenge. In the fields of oceanography and meteorology, the numerical preservation of the so-called geostrophic state, which is the balance between the gravity field and the Coriolis force, can significantly improve the forecasts. In addition, data assimilation is required to improve the simulations and correct the dissipative effect of the numerical scheme.

The sediment transport modelling is of major interest in terms of applications, in particular to estimate the sustainability of facilities with silt or scour, such as canals and bridges. Dredging or filling-up operations are expensive and generally not efficient in the long term. The objective is to determine a configuration almost stable for the facilities. In addition, it is also important to determine the impact of major events like emptying dam which is aimed at evacuating the sediments in the dam reservoir and requires a large discharge. However, the downstream impact should be measured in terms of turbidity, river morphology and flood.

4.3. Hydrological disasters

It is a violent, sudden and destructive flow. Between 1996 and 2005, nearly 80% of natural disasters in the world have meteorological or hydrological origins. The main interest of their study is to predict the areas in which they may occur most probably and to prevent damages by means of suitable amenities. In France, floods are the most recurring natural disasters and produce the worst damages. For example, it can be a cause or a consequence of a dam break. The large surface they cover and the long period they can last require the use of reduced models like the shallow water equations. In urban areas, the flow can be largely impacted by the debris, in particular cars, and this requires fluid/structure interactions be well understood. Moreover, underground flows, in particular in sewers, can accelerate and amplify the flow. To take them into account, the model and the numerical resolution should be able to treat the transition between free surface and underground flows.

Tsunamis are another hydrological disaster largely studied. Even if the propagation of the wave is globally well described by the shallow water model in oceans, it is no longer the case close to the epicenter and in the coastal zone where the bathymetry leads to vertical accretions and produces substantial dispersive effects. The non-hydrostatic terms have to be considered and an efficient numerical resolution should be induced.

While viscous effects can often be neglected in water flows, they have to be taken into account in situations such as avalanches, debris flows, pyroclastic flows, erosion processes, ...*i.e.* when the fluid rheology becomes more complex. Gravity driven granular flows consist of solid particles commonly mixed with an interstitial lighter fluid (liquid or gas) that may interact with the grains and decrease the intensity of their contacts, thus reducing energy dissipation and favoring propagation. Examples include subaerial or subaqueous rock avalanches (e.g. landslides).

4.4. Biodiversity and culture

Nowadays, simulations of the hydrodynamic regime of a river, a lake or an estuary, are not restricted to the determination of the water depth and the fluid velocity. They have to predict the distribution and evolution of external quantities such as pollutants, biological species or sediment concentration.

The potential of micro-algae as a source of biofuel and as a technological solution for CO₂ fixation is the subject of intense academic and industrial research. Large-scale production of micro-algae has potential for biofuel applications owing to the high productivity that can be attained in high-rate raceway ponds. One of the key challenges in the production of micro-algae is to maximize algae growth with respect to the exogenous energy that must be used (paddlewheel, pumps, ...). There is a large number of parameters that need to be optimized (characteristics of the biological species, raceway shape, stirring provided by the paddlewheel). Consequently our strategy is to develop efficient models and numerical tools to reproduce the flow induced by the paddlewheel and the evolution of the biological species within this flow. Here, mathematical models can greatly help us reduce experimental costs. Owing to the high heterogeneity of raceways due to gradients of temperature, light intensity and nutrient availability through water height, we cannot use depth-averaged models. We adopt instead more accurate multilayer models that have recently been proposed. However, it is clear that many complex physical phenomena have to be added to our model, such as the effect of sunlight on water temperature and density, evaporation and external forcing.

Many problems previously mentioned also arise in larger scale systems like lakes. Hydrodynamics of lakes is mainly governed by geophysical forcing terms: wind, temperature variations, ...

4.5. Sustainable energy

One of the booming lines of business is the field of renewable and decarbonated energies. In particular in the marine realm, several processes have been proposed in order to produce electricity thanks to the recovering of wave, tidal and current energies. We may mention water-turbines, buoys turning variations of the water height into electricity or turbines motioned by currents. Although these processes produce an amount of energy which is less substantial than in thermal or nuclear power plants, they have smaller dimensions and can be set up more easily.

The fluid energy has kinetic and potential parts. The buoys use the potential energy whereas the water-turbines are activated by currents. To become economically relevant, these systems need to be optimized in order to improve their productivity. While for the construction of a harbour, the goal is to minimize swell, in our framework we intend to maximize the wave energy.

This is a complex and original issue which requires a fine model of energy exchanges and efficient numerical tools. In a second step, the optimisation of parameters that can be changed in real-life, such as bottom bathymetry and buoy shape, must be studied. Eventually, physical experiments will be necessary for the validation.

4.6. Urban environment

The urban environment is essentially studied for air and noise pollutions. Air pollution levels and noise pollution levels vary a lot from one street to next. The simulations are therefore carried out at street resolution and take into account the city geometry. The associated numerical models are subject to large uncertainties. Their input parameters, e.g. pollution emissions from road traffic, are also uncertain. Quantifying

the simulation uncertainties is challenging because of the high computational costs of the numerical models. An appealing approach in this context is the use of metamodels, from which ensembles of simulations can be generated for uncertainty quantification.

The simulation uncertainties can be reduced by the assimilation of fixed and mobile sensors. High-quality fixed monitoring sensors are deployed in cities, and an increasing number of mobile sensors are added to the observational networks. Even smartphones can be used as noise sensors and dramatically increase the spatial coverage of the observations. The processing and assimilation of the observations raises many questions regarding the quality of the measurements and the design of the network of sensors.

4.7. SmartCity

There is a growing interest for environmental problems at city scale, where a large part of the population is concentrated and where major pollutions can occur. Numerical simulation is well established to study the urban environment, *e.g.* for road traffic modelling. As part of the smartcity movement, an increasing number of sensors collect measurements, at traditional fixed observation stations, but also on mobile devices, like smartphones. They must properly be taken into account given their number but also their potential low quality.

Practical applications include air pollution and noise pollution. These directly relate to road traffic. Data assimilation and uncertainty propagation are key topics in these applications.

ARAMIS Project-Team

4. Application Domains

4.1. Introduction

We develop different applications of our new methodologies to brain pathologies, mainly neurodegenerative diseases. These applications aim at:

- better understanding the pathophysiology of brain disorders;
- designing systems to support clinical decisions such as diagnosis, prognosis and design of clinical trials;
- developing brain computer interfaces for clinical applications.

4.2. Understanding brain disorders

Computational and statistical approaches have the potential to help understand the pathophysiology of brain disorders. We first aim to contribute to better understand the relationships between pathological processes, anatomical and functional alterations, and symptoms. Moreover, within a single disease, there is an important variability between patients. The models that we develop have the potential to identify more homogeneous disease subtypes, that would constitute more adequate targets for new treatments. Finally, we aim to establish the chronology of the different types of alterations. We focus these activities on neurodegenerative diseases: dementia (Alzheimer's disease, fronto-temporal dementia), Parkinson's disease, multiple sclerosis.

4.3. Supporting clinical decisions

We aim to design computational tools to support clinical decisions, including diagnosis, prognosis and the design of clinical trials. The differential diagnosis of neurodegenerative diseases can be difficult. Our tools have the potential to help clinicians by providing automated classification that can integrate multiple types of data (clinical/cognitive tests, imaging, biomarkers). Predicting the evolution of disease in individual patients is even more difficult. We aim to develop approaches that can predict which alterations and symptoms will occur and when. Finally, new approaches are needed to select participants in clinical trials. Indeed, it is widely recognized that, to have a chance to be successful, treatments should be administered at a very early stage.

4.4. Brain computer interfaces for clinical applications

A brain computer interface (BCI) is a device aiming to decode brain activity, thus creating an alternate communication channel between a person and the external environment. BCI systems can be categorized on the basis of the classification of an induced or evoked brain activity. The central tenet of a BCI is the capability to distinguish different patterns of brain activity, each being associated to a particular intention or mental task. Hence adaptation, as well as learning, is a key component of a BCI because users must learn to modulate their brainwaves to generate distinct brain patterns. Usually, a BCI is considered a technology for people to substitute some lost functions. However, a BCI could also help in clinical rehabilitation to recover motor functions. Indeed, in current neuroscience-based rehabilitation it is recognized that protocols based on mental rehearsal of movements (like motor imagery practicing) are a way to access the motor system because they can induce an activation of sensorimotor networks that were affected by lesions. Hence, a BCI based on movement imagery can objectively monitor patients' progress and their compliance with the protocol, monitoring that they are actually imagining movements. It also follows that feedback from such a BCI can provide patients with an early reinforcement in the critical phase when there is not yet an overt sign of movement recovery.

COMMEDIA Project-Team

4. Application Domains

4.1. Cardiovascular hemodynamics

The heart is a double pump whose purpose is to deliver blood to the tissue and organs of the body. This function is made possible through the opening and closing of the heart valves. Cardiac diseases generally manifest by affecting the pumping function of the heart. Numerical simulations of cardiac hemodynamics, in normal and pathological conditions, are recognized as a tool of paramount importance for improving the understanding, diagnosis and treatment of cardiac pathologies, and also for the development of implantable devices (see, e.g., [63], [46]). As an example, we can mention the case of cardiac mitral valve regurgitation, one of the most common heart valve diseases. For this pathology, clinical data are known to be insufficient for determining the optimal timing for surgery, the best surgical strategy and the long-term outcome of a surgical repair. Contrary to imaging techniques, numerical simulations provide local information, such as pressure and stresses, which are of fundamental importance for the prediction of the mechanical behavior of native valves and of implantable devices.

4.2. Respiratory flows

Respiration involves the transport of air through the airways from the mouth to the alveoli of the lungs. These units where diffusion of oxygen and carbon dioxide take place, are surrounded by a viscoelastic medium (the parenchyma) consisting of blood vessels and collagen fibers. Air flows due to the displacement of the diaphragm, which drives the pulmonary parenchyma. Accidental inhalations of foreign bodies or pathologies such as asthma, emphysema and fibrosis might prevent the lung of fulfilling its function. Therapies mostly use aerosols (set of small particles, solid or liquid), which must reach the specific areas of the lung targeted for treatment. Understanding the airflow mechanisms within the respiratory network is a fundamental ingredient for predicting the particles motion and their deposition (see, e.g., [44]). Moreover, understanding of the gas diffusion in the lung is also of major importance since the main function of this organ is to deliver oxygen to the blood.

4.3. Safety pharmacology

The problem of safety pharmacology can be summarized as follows: given a molecule which is a candidate to become a drug, is its use dangerous due to side effects? Among all the different problems to be addressed, one of the most relevant questions in pharmacology is cardio-toxicity (see [58]). More precisely, the objective is to determine whether or not a molecule alters in a significant way the normal functioning of the cardiac cells. To answer these questions, the CiPA initiative promotes the introduction of novel techniques and their standardisation (see [50]). One of the proposed tests of the CiPA panel is to measure the electrical activity using Micro-Electrodes Array: these are microchips that record the electrical activity of an ensemble of cells. The task is to infer the impact of a drug on the ionic currents of each cell based on the electrical signal measured (electrograms) and, in perspective, to be able to assess whether a molecule can induce arrhythmia (see [49]).

MAMBA Project-Team

4. Application Domains

4.1. Introduction

The team has two main application-driven research axes. Applicative axis 1 focuses on cancer, an application on which almost all team members work, with various approaches. A main focus of the team is to study cancer as a Darwinian evolutionary phenomenon in phenotype-structured cell populations. Optimal control methods take into account the two main pitfalls of clinical cancer therapeutics, namely unwanted toxic side effects in healthy cell populations and drug resistance in cancer cell populations. Other studies concern telomere shortening, and multi-scale models. Applicative axis 2 is devoted to growth, evolution and regeneration in populations and tissues. It involves protein aggregation and fragmentation models for neurodegenerative diseases (prion, Alzheimer), organ modeling, mainly of the liver, its damages induced by toxic molecules, and its regeneration after toxic insult. Newcomers in this applicative field are epidemiological modeling of propagation of insect vector-borne diseases by reaction-diffusion equations and of their optimal control, bacterial growth and wound healing.

4.2. Applicative axis 1: Focus on cancer

Personnel

Luis Almeida, Jean Clairambault, Marie Doumic, Dirk Drasdo, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil.

Project-team positioning

The MAMBA team designs and analyses mathematical models of tumor growth and therapy, at the cell population level, using agent-based or partial differential equations, with special interest in methodologies for therapeutic optimization using combined anticancer drug treatments. Rather than, or not only, modeling the effect of drugs on molecular targets, we represent these effects by their functional consequences on the fate of healthy and cancer cell populations: proliferation (velocity of the cell division cycle, decreasing it, e.g., by antagonizing growth factor receptors), apoptosis, cell death or senescence. Our goal in doing this is to circumvent the two main issues of anticancer therapy in the clinic, namely unwanted toxic side effects in populations of healthy cells and emergence of drug-induced drug resistance in cancer cell populations. This point of view leads us to take into account phenomena of transient and reversible resistance, observed in many cancer cell populations, by designing and analyzing models of cell populations structured in continuous phenotypes, relevant for the description of the behavior of cell populations exposed to drugs: either degree of resistance to a given drug, or potential of resistance to drug-induced stress, proliferation potential, and plasticity. Such modeling options naturally lead us to take into account in a continuous way (i.e., by continuous-valued phenotype or relevant gene expression) the wide phenotypic heterogeneity of cancer cell populations. They also lead us to adopt the point of view of adaptive dynamics according to which characteristic traits of cell populations evolve with tumor environmental pressure (drugs, cytokines or metabolic conditions, mechanical stress and spatial conditions), in particular from drug sensitivity to resistance. This position is original on the international scene of teams dealing with drug resistance in cancer.

Scientific achievements

Modeling Acute Myeloid Leukemia (AML) and its control by anticancer drugs by PDEs and Delay Differential equations

In collaboration with Catherine Bonnet (Inria DISCO, Saclay) and François Delhommeau (St Antoine hospital in Paris), together with DISCO PhD students José Luis Avila Alonso and Walid Djema, this theme has led to common published proceedings of conferences: IFAC, ACC, CDC, MTNS [66], [67], [68], [77], [95], [65]. These works study the stability of the haematopoietic system and its possible restabilization by combinations of anticancer drugs with functional targets on cell populations: proliferation, apoptosis, differentiation.

Adaptive dynamics setting to model and circumvent evolution towards drug resistance in cancer by optimal control

We tackle the problem to represent and inhibit - using optimal control algorithms, in collaboration with Emmanuel Trélat, proposed Inria team CAGE - drug-induced drug resistance in cancer cell populations. This theme, presently at the core of our works on cancer modeling with a evolutionary perspective on tumor heterogeneity, is documented in a series of articles [90], [92], [124], [125], [127]. Taking into account the two main pitfalls of cancer therapy, unwanted side effects on healthy cells and evolution towards resistance in cancer cells, it has attracted to our team the interest of several teams of biologists, with whom we have undertaken common collaborative works, funded by laureate answers to national calls (see ITMO Cancer HTE call).

This theme is also at the origin of methodological developments (see Research axis 1). In collaboration with Shensi Shen from Institut Gustave Roussy and Francois Vallette from Université de Nantes, we aim to develop simple non-spatial models to understand the mechanisms of drug resistance acquisition -and loss- in melanoma and glioblastoma. The models are systematically compared with in vitro and in vivo data generated by our collaborators and treated via image processing techniques developed in the team.

Senescence modeling by telomere shortening

In many animals, aging tissues accumulate senescent cells, a process which is beneficial to protect from cancer in the young organism. In collaboration with Teresa Teixeira and Zhou Xu from IBCP, we proposed a mathematical model based on the molecular mechanisms of telomere replication and shortening and fitted it on individual lineages of senescent *Saccharomyces cerevisiae* cells, in order to decipher the causes of heterogeneity in replicative senescence [79].

Biomechanically mediated growth control of cancer cells

Model simulations indicate that the response of growing cell populations on mechanical stress follows a simple universal functional relationship and is predictable over different cell lines and growth conditions despite the response curves look largely different. We developed a hybrid model strategy in which cells were represented by coarse-grained individual units calibrated in a high resolution cell model and parameterized each model cell by measurable biophysical and cell-biological parameters. Cell cycle progression in our model is controlled by volumetric strain, the latter being derived from a bio-mechanical relation between applied pressure and cell compressibility. After parameter calibration from experiments with mouse colon carcinoma cells growing against the resistance of an elastic alginate capsule, the model adequately predicts the growth curve in i) soft and rigid capsules, ii) in different experimental conditions where the mechanical stress is generated by osmosis via a high molecular weight dextran solution, and iii) for other cell types with different growth kinetics. Our model simulation results suggest that the growth response of cell population upon externally applied mechanical stress is the same, as it can be quantitatively predicted using the same growth progression function [123].

Bio-mechanical models of tissue growth

The degenerate Cahn-Hilliard equation is a standard model to describe living tissues. It takes into account cell populations undergoing short-range attraction and long-range repulsion effects. In this framework, we consider the usual Cahn-Hilliard equation with a singular single-well potential and degenerate mobility. These degeneracy and singularity induce numerous difficulties, in particular for its numerical simulation. To overcome these issues, we propose in [hal-02274417] a relaxation system formed of two second order equations which can be solved with standard packages. This system is endowed with an energy and an entropy structure compatible with the limiting equation. Here, we study the theoretical properties of this system; global existence and convergence of the relaxed system to the degenerate Cahn-Hilliard equation. We also study the long-time asymptotics which interest relies on the numerous possible steady states with given mass.

Free boundary multiphase models of tumor growth

Multiphase mechanical models are now commonly used to describe living tissues including tumour growth. The specific model we study here consists of two equations of mixed parabolic and hyperbolic type which extend the standard compressible porous media equation, including cross-reaction terms. We study the incompressible limit, when the pressure becomes stiff, which generates a free boundary problem. We establish the complementarity relation and also a segregation result. Several major mathematical difficulties arise in the two species case which are addressed in [43]. Firstly, the system structure makes comparison principles fail. Secondly, segregation and internal layers limit the regularity available on some quantities to BV. Thirdly, the Aronson-Bénilan estimates cannot be established in our context. We are lead, as it is classical, to add correction terms. This procedure requires technical manipulations based on BV estimates only valid in one space dimension. Another novelty is to establish an L^1 version in place of the standard upper bound.

Philosophy of cancer

The quite natural idea that cancer is a disease of the control of coherent multicellularity, expressed when cohesion of tissues and coherence of (unknown, except maybe for the case of a centralised circadian clock) synchronising signals fail to ensure it, by a regression towards unicellularity, stopping in this “reverse evolution path” at a coarse, incoherent multicellularity state⁰ continues to be developed and popularised by Jean Clairambault in seminars and workshops, and published in review articles [13], [45]. This view, and the investigation of the immune system in the design of such coherence of all multicellular organisms⁰ is naturally inscribed in a *philosophy of cancer* perspective, and from a mathematical viewpoint, to multicellularity genes - and links between them and unicellularity genes - seen as a *hyperstructure*⁰ above structures consisting of the genes of unicellularity, i.e., those that make a single cell a coherent living system, such hyperstructure being failed in cancer; this view is presently under development with colleagues from universities of the Paris region, together with Nils Baas at NTNU, Trondheim, Norway). This perspective, that makes use of category theory as a structuring point of view to apprehend multicellularity and cancer, is also meant to endow us with an innovative methodology to apply *topological data analysis (TDA)* to investigate cancer genome data.

Modelling of TMZ induced drug resistance

Temozolomide (TMZ) is a standard chemotherapy treatment in patients with glioblastoma. Resistance to this drug is correlated to the presence of a specific enzyme, which activity in cancer cells creates a drug-induced cell death resistant phenotype. Understanding the transition of cancer cells to a resistant phenotype is still a topic of research where multiple hypothesis have been studied: From an adaptive process to an inherent resistance to treatment. Moreover it has been recently shown that TMZ treatment has an influence on the spatial structuration of cancer cell aggregates. In the frame of the HTE project MoGIIImaging and through the recent hiring of a post-doctoral candidate (Gissell Estrada Rodriguez), we are currently developing a mathematical framework to study and analyse the evolution of a population of glioblastoma cells that are exposed to TMZ. Based on the experimental data generated by our partner team led by F. Valette (Inserm Nantes), we propose a Keller-Segel type model for the formation of spheroid as a result of a chemoattractant produced by cancer cells, and study the influence of a chemotherapeutic agent on the structuration of the cancer cell aggregates. By confronting the model results to experimental data, different modelling choices are currently explored to identify which key mechanisms could be responsible for the apparition of drug resistance in glioblastoma.

Collaborations

- AML modelling: **Catherine Bonnet**, DISCO Inria team, Saclay, and **François Delhommeau**, INSERM St Antoine (also collaborator in the INSERM HTE laureate project EcoAML, see below).
- INSERM HTE laureate project MoGIIImaging, headed by E. Moyal (Toulouse): **François Vallette**, CRCNA and INSERM Nantes
- INSERM HTE laureate project EcoAML, headed by **François Delhommeau**, INSERM St Antoine: François Delhommeau, Thierry Jaffredo (IBPS), Delphine Salort (LCQB-IBPS)
- Adaptive dynamics to model drug resistance and optimal control to circumvent it:

⁰Metazoa 1.0, as theorised by PCW Davies and CH Lineweaver in their article “Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors”, Physical Biology 2011, that popularised the so-called atavistic hypothesis of cancer

⁰this latter point partly, however nicely, developed in Thomas Pradeu’s book “The limits of the self”, OUP 2012

⁰See on this point, e.g., Nils Baas: “On the philosophy of higher structures”, Int. J. General Systems 2019

Alexandre Escargueil, Michèle Sabbah (1 PhD thesis in common), St Antoine Hospital, Paris

Emmanuel Trélat (1 PhD thesis in common) at Inria team CAGE and Laboratoire Jacques-Louis Lions at Sorbonne Université.

Frédéric Thomas at CREEC, Montpellier.

Tommaso Lorenzi (Univ. of St Andrews).

- Telomere shortening: **Teresa Teixeira** and **Zhou Xu** (IBCP, Paris), **Philippe Robert** (Inria RAP).
- TRAIL treatment: **Gregory Batt**, Inria Saclay and Inst. Pasteur (France)
- Biomechanical control of cancer cells: **Pierre Nassoy**, Bioimaging and Optofluidics Group, LP2N – UMR 5298, IOGS, CNRS & University of Bordeaux

4.3. Applicative axis 2: Growth, evolution and regeneration in populations and tissues

Luis Almeida, Pierre-Alexandre Bliman, Marie Doumic, Dirk Drasdo, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil, Philippe Robert

Project-team positioning

The applications in this category span very different subjects from amyloid diseases, dengue fever, wound healing, liver regeneration and toxicity, up to bacterial growth and development of organisms. As the applications, the methods span a wide range. Those concerning identification of models and parameters with regard to data have partially been outlined in axis 3. Focus in this axis is on the model contribution to the biologically and/or medically relevant insights and aspects.

Liver-related modelling is partially performed within the Inria team MIMESIS (Strasbourg) with the focus on real-time, patient-specific biomechanical liver models to guide surgery and surgeons. Internationally, spatial temporal liver related models are developed in Fraunhofer MEVIS (Bremen), by T. Ricken (TU Dortmund), and P. Segers group (Leuven).

Different from these, Mamba has a strong focus on spatial-temporal modeling on the histological scale, integration of molecular processes in each individual cell, and single-cell (agent) based models [102]. Works by Schliess [149], [107] have been highlighted in editorials.

Mathematical modeling of protein aggregation is a relatively recent domain, only a few other groups have emerged yet; among them we can cite the Inria team Dracula, with whom we are in close contact, and e.g., the work by Jean-Michel Coron (Sorbonne Université) and Monique Chyba (Hawaii, USA) in control, and Suzanne Sindi (USA) for the modeling of the yeast prion. We have interactions with all these groups and organized a workshop in June 2017, gathering both the biophysics and applied mathematics communities.

Scientific achievements

Amyloid disease

Application to protein aggregation in amyloid diseases is a long-standing interest of Mamba, dating back to 2010 [85], and developed through the collaboration with Human Rezaei's team at Inria. More recently, with Wei-Feng Xue in Canterbury, we investigated the intrinsic variability among identical experiments of nucleation [98], [106], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [105].

In collaboration with Tom Banks first [70], [69] and then Philippe Moireau, we developed quantitative comparisons between model and data. Through data assimilation and statistical methods [63], we proposed new models and mechanisms.

Biological control of arboviruses

Sterile Insect Technique (SIT) [104] is a biological control method relying on massive releases of sterile male insects into the wild. The latter compete with wild males to mate with the females, and induce no offspring to the latter, thus reducing the next generation's population. This can result in a progressive reduction, or even disparition, of the target population.

A related technique is based on the infection by *Wolbachia* [111]. This symbiotic bacterium is maternally transmitted from infected females to their offspring, but induces *cytoplasmic incompatibility* [151], [80]: mating between infected males and uninfected females gives no offspring. Releases of *Wolbachia* infected males alone is thus comparable to classical SIT.

On the other hand, releasing both infected males and females in sufficient quantity may result in infection of the wild population. This gives rise to an interesting new control principle, as *Wolbachia* has been shown to severely reduce the insect vectorial ability to transmit dengue, zika or chikungunya, indirectly by lifespan and fertility reduction, and directly by reducing the ability of the viruses to proliferate within the organism [130].

We proposed new insights on the practical and theoretical issues raised by the implementation of the previous methods. Concerning the SIT, we obtained control synthesis results through impulsive periodic release of controlled amplitude [10], and through optimal control approach [42]. Concerning *Wolbachia* technique, we investigated general control principles [39] capable of spreading the infection.

Wound healing 1: epithelial tissues

We studied cell motion in epithelial gap closure, a form of collective cell migration that is a very widespread phenomenon both during development and adult life - it is essential for both the formation and for the maintenance of epithelial layers. Due to their importance, *in vivo* wound healing and morphogenetic movements involving closure of holes in epithelia have been the object of many studies. In our works ⁰ we considered wound healing and epithelial gap closure in both *in vivo* (in particular *Drosophila* pupa) and *in vitro* (MDCK cell and human keratinocytes). We found some similarities in the geometry dependence of the wound closure strategies between these two situations, indicating the existence of conserved mechanisms that should be widespread across living beings. We are concentrating on the study of actin cable formation.

Wound healing 2: adipose tissues

After injury, if regeneration can be observed in hydra, planaria and some vertebrates, regeneration is rare in mammals and particularly in humans. In this research axis, we investigated the mechanisms by which biological tissues recover after injury. We explored this question on adipose tissue, using the mathematical framework recently developed in [144]. Our assumption is that simple mechanical cues between the Extra-Cellular Matrix (ECM) and differentiated cells can explain adipose tissue morphogenesis and that regeneration requires after injury the same mechanisms. We validated this hypothesis by means of a two-dimensional Individual Based Model (IBM) of interacting adipocytes and ECM fiber elements [145]. The model successfully generated regeneration or scar formation as functions of few key parameters, and seemed to indicate that the fate of injury outcome could be mainly due to ECM rigidity.

Following these encouraging results, the team is currently taking a step further in the model validation and confrontation to experimental data. The first direction concerns the development of a 3D framework to validate the mechanisms observed in 2D. In collaboration with S. Merino-Aceituno from the University of Vienna, efforts are being made in the development of a complete synthetic tissue model coupling the ECM and cell modelling with a vascularization model. A PhD project has been started to implement the coupled models and reduce the CPU time with the long-term goal to develop a usable software which would serve to investigate the role of different mechanisms in tissue development (not restricted to adipose tissues). Finally, further developments in collaboration with Imperial College London aim at pursuing the derivation of macroscopic PDE models from the agent-based formalisms.

Mathematical modelling of axolotl regeneration

Tissue response after injury/amputation induces one or two alternatives: scar formation versus regeneration (complete recovery of tissue shape and functions). In most mammals, regeneration is considered largely impaired for the benefit of a fibrotic scar after injury automatically associated with dysfunctions, but complete regeneration has been largely described and investigated in animal models such as zebra fish, salamander, or axolotl. Despite several processes regulating regeneration have been identified at different scales -from diffusing molecules and cellular gene expression patterns up to tissue mechanics-, how these mechanisms individually or collectively play a role in the regulation of regenerative processes remains poorly understood.

⁰[ravasio:hal-01245750](https://arxiv.org/abs/ravasio:hal-01245750), [vedula:hal-01298859](https://arxiv.org/abs/vedula:hal-01298859)

In order to give insights into the mechanisms of tissue regeneration, Valeria Caliaro started an Inria PhD project in October 2019, in collaboration with Osvaldo Chara, internationally recognized group leader of SysBio in Argentina. This project focuses on the role of cell proliferation in space and time along the two first phases of regeneration after injury: (i) initiation of a regeneration response, (ii) tissue patterning during regenerate growth. The first part of the project aims at building an agent-based model featuring few key mechanisms regulating cell proliferation after injury. The model construction is based on recent works where the authors developed a mathematical model given by ordinary differential equations (ODEs) [2] and a mathematical framework in 1D [3] showing that acceleration of the cell cycle is the major driver of regenerative spinal cord outgrowth in axolotls. Building on both mathematical models and introducing heuristic rules which rely on Prof O. Chara expertise, we propose a 2D-ABM using methodologies borrowed from socio-dynamics and collective behavior studies (based on many interacting agent systems). While the focus is made on proliferation-based mechanisms, other mechanisms responsible for collective behavior such as volume exclusion, diffusion or aggregation will be tested and compared with experimental data. The resulting model will provide a synthetic tissue model which will serve to investigate regeneration in cellular systems, focusing on cell proliferation properties. The second part of the PhD will be devoted to the derivation of continuous models from the agent-based formalism. This will provide a large scale ‘synthetic tissue’ model to explore the role of large scale effects in general tissue models. Model validation and calibration will be ensured by quantitative comparison with biological data already present in the literature and generated by the SysBio group of O. Chara, particularly the representative images of regenerative spinal cords after tail amputation. By varying the model parameters and observing the resulting alteration of the spinal cord size and architecture as a consequence of these variations, it will be possible to provide ‘in silico’ setting experiments to guide and plan future in vivo or ex vivo experiments. Altogether, the project is expected to provide a mechanistic understanding of the cellular mechanisms driving spinal cord regeneration, and to identify how spatial structuration can influence cell differentiation and growth.

[1] Rodrigo Albors A, Tazaki A, Rost F, Nowoshilow S, Chara O & Tanaka EM. 2015. Planar cell polarity-mediated induction of neural stem cell expansion during axolotl spinal cord regeneration. *Elife*. 4:e10230. [2] Rost F, Rodrigo Albors A, Mazurov V, Brusch L, Deutsch A, Tanaka EM & Chara O. 2016. Accelerated cell divisions drive the outgrowth of the regenerating spinal cord in axolotls. *Elife*. 5. pii: e20357. [3] Cura Costa E, Rodrigo Albors A, Tanaka EM & Chara O. Spatiotemporal distribution of cell proliferation rules spinal cord regeneration in the axolotl. MS in preparation.

Quantitative cell-based model predicts mechanical stress response of growing tumor spheroids

Model simulations indicate that the response of growing cell populations on mechanical stress follows the same functional relationship and is predictable over different cell lines and growth conditions despite experimental response curves look largely different. We developed a hybrid model strategy in which cells are represented by coarse-grained individual units calibrated with a high resolution cell model and parameterized by measurable biophysical and cell-biological parameters. Cell cycle progression in our model is controlled by volumetric strain, the latter being derived from a bio-mechanical relation between applied pressure and cell compressibility. After parameter calibration from experiments with mouse colon carcinoma cells growing against the resistance of an elastic alginate capsule, the model adequately predicts the growth curve in i) soft and rigid capsules, ii) in different experimental conditions where the mechanical stress is generated by osmosis via a high molecular weight dextran solution, and iii) for other cell types with different growth kinetics from the growth kinetics in absence of external stress. Our model simulation results suggest a generic, even quantitatively same, growth response of cell populations upon externally applied mechanical stress, as it can be quantitatively predicted using the same growth progression function ([52])

Modeling of morphogen diffusion in *Drosophila* oogenesis

In collaboration with a team of developmental biologists of Rutgers University (Camden, New Jersey), we have built a model for the diffusion of the Gurken morphogen during *Drosophila* oogenesis, taking into account a wide variety of biological mechanisms such as diffusion of the morphogen, reactions of components of the EGFR signaling pathway, movement of the source of morphogen, shift of the overlying follicle cells and growth of the egg chamber. This model, together with a complete numerical code developed in Matlab,

provides a tool to understand how each mechanism influences the signal distribution. The overall aim of the project is to use this tool to guide future experiments, and to understand what mechanisms contribute to the different distributions of signal among species.

Bacterial population growth

We exploited all the methods developed to estimate the division rate of a population (see axis 3) to address a seminal question of biology: is it a size-sensing or a timing mechanism which triggers bacterial growth? In [148], we showed that a sizer model is robust and fits the data well. Several studies from other groups came at the same time, showing a renewed interest on a question dated back to Jacques Monod's PhD thesis (1941). Of special interest is the "adder" model, for which we are currently developing new estimation methods [46].

A quantitative high resolution computational mechanics cell model for growing and regenerating tissues

Mathematical models are increasingly designed to guide experiments in biology, biotechnology, as well as to assist in medical decision making. They are in particular important to understand emergent collective cell behavior. For this purpose, the models, despite still abstractions of reality, need to be quantitative in all aspects relevant for the question of interest. Considered as a showcase example the regeneration of liver after drug-induced depletion of hepatocytes, in which the surviving and dividing hepatocytes must squeeze in between the blood vessels of a network to refill the emerged lesions. Here, the cells' response to mechanical stress might significantly impact the regeneration process. We present a 3D high-resolution cell-based model integrating information from measurements in order to obtain a refined and quantitative understanding of the impact of cell-biomechanical effects on the closure of drug-induced lesions in liver. Our model represents each cell individually and is constructed by a discrete, physically scalable network of viscoelastic elements, capable of mimicking realistic cell deformation and supplying information at subcellular scales. The cells have the capability to migrate, grow, and divide, and the nature and parameters of their mechanical elements can be inferred from comparisons with optical stretcher experiments. Due to triangulation of the cell surface, interactions of cells with arbitrarily shaped (triangulated) structures such as blood vessels can be captured naturally. Comparing our simulations with those of so-called center-based models, in which cells have a largely rigid shape and forces are exerted between cell centers, we find that the migration forces a cell needs to exert on its environment to close a tissue lesion, is much smaller than predicted by center-based models. To stress generality of the approach, the liver simulations were complemented by monolayer and multicellular spheroid growth simulations. In summary, our model can give quantitative insight in many tissue organization processes, permits hypothesis testing in silico, and guide experiments in situations in which cell mechanics is considered important [123].

Liver regeneration and disease: towards a full virtual liver model at histological scale

In our work towards a full virtual liver model at histological level, a number of steps were performed. The models under points (1)-(4) focus on either a single or a few liver lobules. A liver lobule is the smallest repetitive functional and anatomical building block of liver, while (5) addresses a much larger organisational building block of the liver, a liver lobe that consists of thousands to hundreds of thousands of lobules depending on the species. A second strand (6), (7) addresses image analysis, which in most cases forms the entrance to modeling as it provides the data necessary to generate model hypotheses and to parameterize a model.

(1) Cell types: In a former work by Hoehme et. al. ([113]) a model of liver regeneration after drug-induced damage was established considering hepatocytes and blood vessels. This model has now been expanded to include all relevant cell types, including hepatocytes, blood vessels, hepatic stellate cells, Kupffer cells, invading macrophages and other immune cells. Thereby it is now possible to study perturbations in the temporal scenario of damage and regeneration after signaling events or cells types are knocked down individually or collectively. This model is currently compared to respective perturbation experiments.

(2) Liver disease: Degenerative liver diseases such as liver fibrosis and cirrhosis develop out of a disturbed balance of degenerative and regenerative processes. The model under (1) has thereby been extended by the formation of extracellular matrix, mimicked as fiber networks, to capture the disease process leading to liver fibrosis. In that process characteristic streets form that modify the mechanics, perfusion behavior and detoxification capacity of the liver.

(3) Consequence of liver fibrosis: Whole-slide scans from fibrotic liver in a mouse model has been analysed at different time points after emergence of the disease with regard to the degree of excess matrix to mimic the possible consequences of fibrotic inclusions on perfusion and function of liver within a multiscale model that considers ammonia detoxification in each individual hepatocyte as well as blood flow and transport processes in the liver lobule.

(4) Bile flux: Bile flux has been for decades believed to be controlled by convection at the level of liver lobules as well as at the level of the entire organ. By a methodology based on correlative imaging for quantitative intravital flux analysis no directed advection was detectable in bile canaliculi at the resolution limit. Instead, after active transport across hepatocyte membranes bile salts within the liver lobules are transported in the canaliculi by a diffusion-dominated process. Only in the interlobular ducts i.e., at super-lobular level, diffusion is augmented by advection. In silico simulations of bile transport in real 3D bile network microarchitectures can quantitatively explain the data assuming diffusive transport as sole mechanism.

(5) Liver regeneration after partial hepatectomy (partial organ removal): Partial hepatectomy is an adequate therapy in case of diseases or events that destructed only part of the liver. A typical case is a primary tumor or a metastasis affecting only a single liver lobe. Within an biophysical agent-based model capturing many aspects of the cell mechanics we studied regrowth of liver after partial organ removal in mouse calibrated with multivariate experimental data. Our model predicts characteristic proliferation pattern that change from small animals (as mouse) to large animals (as pig).

(6) Bile duct ligation: Bile duct ligation (BDL) is an experimental procedure that mimics obstructive cholestatic disease. One of the early consequences of BDL in rodents is the appearance of so-called bile infarcts that correspond to Charcot-Gombault necrosis in human cholestasis. The mechanisms causing bile infarcts and their pathophysiological relevance are unclear. Therefore, intravital two photon-based imaging of BDL mice was performed with fluorescent bile salts (BS) and non-BS organic anion analogues. Key findings were followed up by matrix-assisted laser desorption ionization imaging, clinical chemistry, immunostaining, and gene expression analyses. Our group performed analysis of intravital imaging. The key finding is that bile microinfarcts occur in the acute phase after BDL in a limited number of dispersed hepatocytes followed by larger infarcts involving neighboring hepatocytes, and they allow leakage of bile from the BS-overloaded biliary tract into blood, thereby protecting the liver from BS toxicity; in the chronic phase after BDL, reduced sinusoidal BS uptake is a dominant protective factor, and the kidney contributes to the elimination of BS until cholemic nephropathy sets in [108].

(7) Periportalisation during liver fibrosis formation: Within a liver lobule, the function of hepatocytes is zoned i.e., certain functions are only executed by either hepatocytes close to the center (pericentral region) or hepatocytes in the periphery of the lobule (periportal region). Little is known about how liver fibrosis influences lobular zonation. To address this question, three mouse models of liver fibrosis were used, CCl₄ administration repeated for 2, 6 and 12 months to induce pericentral damage, as well as bile duct ligation (21 days) and a particular *mdr2*-mouse model to study periportal fibrosis. Analyses were performed by RNA-sequencing, immunostaining of zoned proteins and image analysis. Image analysis was performed by our group. The key result was that liver fibrosis leads to strong alterations of lobular zonation, where the pericentral region adopts periportal features. Beside adverse consequences, periportalization supports adaptation to repeated doses of hepatotoxic compounds [17].

Toxicity extrapolation from in vitro to in vivo

In vivo toxicity prediction from in vitro data is a major objective in toxicology as it permits bypassing animal experiments, and as the predictive power of animal experiments for human is limited. Objective was the prediction of paracetamol (acetaminophen)-induced hepatotoxicity from in vitro experiments. For this purpose, numerous iterations between in vitro experiments, in vivo experiments and simulations were performed for mouse. Using a recent thesis (Géraldine Cellière's PhD thesis [88]) as a start point, two candidate mechanisms could be identified both explaining the in vivo data after calibration of the in silico model with in vitro toxicity data.

Relating imaging on microscopic scales with imaging on macroscopic scales: From Diffusion-Weighted MRI Calibrated With Histological Data: an Example From Lung Cancer

Diffusion-weighted magnetic resonance imaging (DWI) is a key non-invasive imaging technique for cancer diagnosis and tumor treatment assessment, reflecting Brownian movement of water molecules in tissues. Since densely packed cells restrict molecule mobility, tumor tissues produce usually higher signal (less attenuated signal) on isotropic maps compared with normal tissues. However, no general quantitative relation between DWI data and the cell density has been established. In order to link low-resolution clinical cross-sectional data with high resolution histological information, we developed an image processing and analysis chain, which was used to study the correlation between the diffusion coefficient (D value) estimated from DWI and tumor cellularity from serial histological slides of a resected non-small cell lung cancer tumor. Color deconvolution followed by cell nuclei segmentation was performed on digitized histological images to determine local and cell-type specific 2d (two-dimensional) densities. From these, the 3d cell density was inferred by a model-based sampling technique, which is necessary for the calculation of local and global 3d tumor cell count. Next, DWI sequence information was overlaid with high resolution CT data and the resected histology using prominent anatomical hallmarks for co-registration of histology tissue blocks and non-invasive imaging modalities' data. The integration of cell numbers information and DWI data derived from different tumor areas revealed a clear negative correlation between cell density and D value. Importantly, spatial tumor cell density can be calculated based on DWI data. In summary, our results demonstrate that tumor cell count and heterogeneity can be predicted from DWI data, which may open new opportunities for personalized diagnosis and therapy optimization [157]. The work of that paper has been further advanced to adapt the procedures for clinical use (in preparation).

Collaborations

- Biological control of arboviruses: **Nicolas Vauchelet** (Université Paris 13); **Grégoire Nadin** (LJLL, Sorbonne Université); **Yannick Privat** (Université de Strasbourg); **D. Villela**, **C. Struchiner** (Fiocruz, Brazil); **Jorge Zubelli** (IMPA, Brazil); **Alain Rapaport** (INRA-Montpellier), **Y. Dumont** (CIRAD-Montpellier); **Ch. Schaerer**, **P. Pérez-Estigarribia** (UNA, Paraguay), **O. Vasilieva** (Universidad del Valle, Cali, Colombia), **D. Cardona-Salgado** (Universidad Autónoma de Occidente, Cali, Colombia).
- Protein aggregation in amyloid diseases: **Human Rezaei**'s team at Inra Jouy-en-Josas (France) and **W-F Xue**'s team in at university of Kent (Great Britain); **Tom Banks** at the North Carolina State University (USA) and **Philippe Moireau** (M3DISIM)
- Bacterial growth and division: **Lydia Robert**, Sorbonne Université (France)
- Liver research & toxicology: **JG. Hengstler** group (IfADo, Dortmund, Germany); **R. Gebhardt** (Univ. Leipzig); **U. Klingmueller** (DKFZ, Heidelberg); **Irène Vignon-Clementel** (Inria, COMME-DIA)
- Growth in capsules and biomechanics: **Pierre Nassoy**, Institut dOptique Graduate School, Talence, France; **Josef Kaes**, Peter Debye Institute for Soft Matter Physics, Physics, Univ. Leipzig, Germany.
- Wound healing: **Patrizia Bagnerini** (Genova, Numerical methods), **Benoît Ladoux** (Institut Jacques Monod et Mechanobiology Institute Singapore, Biophysics) and **Antonio Jacinto** (CEDOC, Lisbon, Biology and Medicine). (Adipose tissue regeneration) team of **L. Casteilla** (StromaLab, Toulouse). (Axolotl regeneration) team of O. Chara, SysBio group, Argentina.
- Diffusion of morphogen: Center for Computational and Integrative Biology, Rutgers University (Camden, New Jersey), joint work with Professor Nir Yakoby's Drosophila Laboratory
- Linking micro and macro-image information: Oliver Sedlacek, Univ. and DKFZ Heidelberg, Kai Breuhahn, Univ. Heidelberg.

REO Team

4. Application Domains

4.1. Blood flows

Cardiovascular diseases like atherosclerosis or aneurysms are a major cause of mortality. It is generally admitted that a better knowledge of local flow patterns could improve the treatment of these pathologies (although many other biophysical phenomena obviously take place in the development of such diseases). In particular, it has been known for years that the association of low wall shear stress and high oscillatory shear index give relevant indications to localize possible zones of atherosclerosis. It is also known that medical devices (graft or stent) perturb blood flows and may create local stresses favorable with atherogenesis. Numerical simulations of blood flows can give access to this local quantities and may therefore help to design new medical devices with less negative impacts. In the case of aneurysms, numerical simulations may help to predict possible zones of rupture and could therefore give a guide for treatment planning.

In clinical routine, many indices are used for diagnosis. For example, the size of a stenosis is estimated by a few measures of flow rate around the stenosis and by application of simple fluid mechanics rules. In some situations, for example in the case a sub-valvular stenosis, it is known that such indices often give false estimations. Numerical simulations may give indications to define new indices, simple enough to be used in clinical exams, but more precise than those currently used.

It is well-known that the arterial circulation and the heart (or more specifically the left ventricle) are strongly coupled. Modifications of arterial walls or blood flows may indeed affect the mechanical properties of the left ventricle. Numerical simulations of the arterial tree coupled to the heart model could shed light on this complex relationship.

One of the goals of the REO team is to provide various models and simulation tools of the cardiovascular system. The scaling of these models will be adapted to the application in mind: low resolution for modeling the global circulation, high resolution for modeling a small portion of vessel.

4.2. Respiratory tracts

Breathing, or “external” respiration (“internal” respiration corresponds to cellular respiration) involves gas transport through the respiratory tract with its visible ends, nose and mouth. Air streams then from the pharynx down to the trachea. Food and drink entry into the trachea is usually prevented by the larynx structure (epiglottis). The trachea extends from the neck into the thorax, where it divides into right and left main bronchi, which enter the corresponding lungs (the left being smaller to accommodate the heart). Inhaled air is then convected in the bronchus tree which ends in alveoli, where gaseous exchange occurs. Surfactant reduces the surface tension on the alveolus wall, allowing them to expand. Gaseous exchange relies on simple diffusion on a large surface area over a short path between the alveolus and the blood capillary under concentration gradients between alveolar air and blood. The lungs are divided into lobes (three on the right, two on the left) supplied by lobar bronchi. Each lobe of the lung is further divided into segments (ten segments of the right lung and eight of the left). Inhaled air contains dust and debris, which must be filtered, if possible, before they reach the alveoli. The tracheobronchial tree is lined by a layer of sticky mucus, secreted by the epithelium. Particles which hit the side wall of the tract are trapped in this mucus. Cilia on the epithelial cells move the mucous continually towards the nose and mouth.

Each lung is enclosed in a space bounded below by the diaphragm and laterally by the chest wall and the mediastinum. The air movement is achieved by alternately increasing and decreasing the chest pressure (and volume). When the airspace transmural pressure rises, air is sucked in. When it decreases, airspaces collapse and air is expelled. Each lung is surrounded by a pleural cavity, except at its hilum where the inner pleura give birth to the outer pleura. The pleural layers slide over each other. The tidal volume is nearly equal to 500 *ml*.

The lungs may fail to maintain an adequate supply of air. In premature infants surfactant is not yet active. Accidental inhalation of liquid or solid and airway infection may occur. Chronic obstructive lung diseases and lung cancers are frequent pathologies and among the three first death causes in France.

One of the goals of REO team in the ventilation field is to visualize the airways (virtual endoscopy) and simulate flow in image-based 3D models of the upper airways (nose, pharynx, larynx) and the first generations of the tracheobronchial tree (trachea is generation 0), whereas simple models of the small bronchi and alveoli are used (reduced-basis element method, fractal homogenization, multiphysics homogenization, lumped parameter models), in order to provide the flow distribution within the lung segments.

4.3. Cardiac electrophysiology

The purpose is to simulate the propagation of the action potential in the heart. A lot of works has already been devoted to this topic in the literature (see *e.g.* [30], [34], [33] and the references therein), nevertheless there are only very few studies showing realistic electrocardiograms obtained from partial differential equations models. Our goal is to find a compromise between two opposite requirements: on the one hand, we want to use predictive models, and therefore models based on physiology, on the other hand, we want to use models simple enough to be parametrized (in view of patient-specific simulations). One of the goal is to use our ECG simulator to address the inverse problem of electrocardiology. In collaboration with the Macs/M3disym project-team, we are interested in the electromechanical coupling in the myocardium. We are also interested in various clinical and industrial issues related to cardiac electrophysiology, in particular the simulation of experimental measurement of the field potential of cardiac stem cells in multi-electrode arrays.

SERENA Project-Team

4. Application Domains

4.1. Multiphase flows and transport of contaminants in the subsurface

- subsurface depollution after chemical leakage
- nuclear waste disposal in deep underground repositories
- flow in large scale discrete fracture networks
- production of oil and gas

4.2. Industrial risks in energy production

- Stokes and Navier–Stokes flows related to nuclear reactor operation
- seismic wave propagation for detection and protection
- electromagnetism for interfaces between dielectrics and negative metamaterials

4.3. Nonlinear mechanics

- quasi-static and dynamic elastoplastic evolutions with small and large deformations
- quasi-static and dynamic crack propagation
- nonlinear contact and friction conditions
- application to engineering components mainly related to nuclear reactor operation and safety analysis

4.4. Computational quantum chemistry

- guaranteed bounds for ground-state energy (eigenvalues) and ground-state density matrix (eigenvectors) in first-principle molecular simulation
- application to Laplace, Gross–Pitaevskii, Kohn–Sham, and Schrödinger models

ALPINES Project-Team

4. Application Domains

4.1. Compositional multiphase Darcy flow in heterogeneous porous media

We study the simulation of compositional multiphase flow in porous media with different types of applications, and we focus in particular on reservoir/bassin modeling, and geological CO₂ underground storage. All these simulations are linearized using Newton approach, and at each time step and each Newton step, a linear system needs to be solved, which is the most expensive part of the simulation. This application leads to some of the difficult problems to be solved by iterative methods. This is because the linear systems arising in multiphase porous media flow simulations cumulate many difficulties. These systems are non-symmetric, involve several unknowns of different nature per grid cell, display strong or very strong heterogeneities and anisotropies, and change during the simulation. Many researchers focus on these simulations, and many innovative techniques for solving linear systems have been introduced while studying these simulations, as for example the nested factorization [Appleyard and Cheshire, 1983, SPE Symposium on Reservoir Simulation].

4.2. Inverse problems

We focus on methods related to the blend of time reversal techniques and absorbing boundary conditions (ABC) used in a non standard way. Since the seminal paper by [M. Fink et al., Imaging through inhomogeneous media using time reversal mirrors. *Ultrasonic Imaging*, 13(2):199, 1991.], time reversal is a subject of very active research. The principle is to back-propagate signals to the sources that emitted them. The initial experiment was to refocus, very precisely, a recorded signal after passing through a barrier consisting of randomly distributed metal rods. In [de Rosny and Fink. Overcoming the diffraction limit in wave physics using a time-reversal mirror and a novel acoustic sink. *Phys. Rev. Lett.*, 89 (12), 2002], the source that created the signal is time reversed in order to have a perfect time reversal experiment. In [39], we improve this result from a numerical point of view by showing that it can be done numerically without knowing the source. This is done at the expense of not being able to recover the signal in the vicinity of the source. In [40], time dependent wave splitting is performed using ABC and time reversal techniques. We now work on extending these methods to non uniform media.

All our numerical simulations are performed in FreeFem++ which is very flexible. As a byproduct, it enables us to have an end user point of view with respect to FreeFem++ which is very useful for improving it.

4.3. Numerical methods for wave propagation in multi-scale media

We are interested in the development of fast numerical methods for the simulation of electromagnetic waves in multi-scale situations where the geometry of the medium of propagation may be described through characteristic lengths that are, in some places, much smaller than the average wavelength. In this context, we propose to develop numerical algorithms that rely on simplified models obtained by means of asymptotic analysis applied to the problem under consideration.

Here we focus on situations involving boundary layers and *localized* singular perturbation problems where wave propagation takes place in media whose geometry or material characteristics are submitted to a small scale perturbation localized around a point, or a surface, or a line, but not distributed over a volumic sub-region of the propagation medium. Although a huge literature is already available for the study of localized singular perturbations and boundary layer phenomena, very few works have proposed efficient numerical methods that rely on asymptotic modeling. This is due to their functional framework that naturally involves singular functions, which are difficult to handle numerically. The aim of this part of our research is to develop and analyze numerical methods for singular perturbation methods that are prone to high order numerical approximation, and robust with respect to the small parameter characterizing the singular perturbation.

4.4. Data analysis in astrophysics

We focus on computationally intensive numerical algorithms arising in the data analysis of current and forthcoming Cosmic Microwave Background (CMB) experiments in astrophysics. This application is studied in collaboration with researchers from University Paris Diderot, and the objective is to make available the algorithms to the astrophysics community, so that they can be used in large experiments.

In CMB data analysis, astrophysicists produce and analyze multi-frequency 2D images of the universe when it was 5% of its current age. The new generation of the CMB experiments observes the sky with thousands of detectors over many years, producing overwhelmingly large and complex data sets, which nearly double every year therefore following Moore's Law. Planck (<http://planck.esa.int/>) is a keystone satellite mission which has been developed under auspices of the European Space Agency (ESA). Planck has been surveying the sky since 2010, produces terabytes of data and requires 100 Petaflops per image analysis of the universe. It is predicted that future experiments will collect on the order of petabyte of data around 2025. This shows that data analysis in this area, as many other applications, will keep pushing the limit of available supercomputing power for the years to come.

4.5. Molecular simulations

Molecular simulation is one of the most dynamic areas of scientific computing. Its field of application is very broad, ranging from theoretical chemistry and drug design to materials science and nanotechnology. It provides many challenging problems to mathematicians and computer scientists.

In the context of the ERC Synergy Grant EMC2 we address several important limitations of state of the art molecular simulation. In particular, the simulation of very large molecular systems, or smaller systems in which electrons interact strongly with each other, remains out of reach today. In an interdisciplinary collaboration between chemists, mathematicians and computer scientists, we focus on developing a new generation of reliable molecular simulation algorithms and software.

DELYS Project-Team (section vide)

DYOGENE Project-Team

4. Application Domains

4.1. Physical communication networks

Internet, wireless, mobile, cellular networks, transportation networks, distributed systems (cloud, call centers).
In collaboration with Nokia Bell Labs and Orange Labs.

4.2. Abstract networks

Social interactions, human communities, economic networks.

4.3. Power grids

Energy networks. In collaboration with EDF.

EVA Project-Team

4. Application Domains

4.1. Industrial Process Automation

Wireless networks have become ubiquitous and are an integral part of our daily lives. These networks are present in many application domains; the most important are detailed in this section.

Networks in industrial process automation typically perform **monitoring and control** tasks. Wired industrial communication networks, such as HART⁰, have been around for decades and, being wired, are highly reliable. Network administrators tempted to “go wireless” expect the same reliability. Reliable process automation networks – especially when used for control – often impose stringent latency requirements. Deterministic wireless networks can be used in critical systems such as control loops, however, the unreliable nature of the wireless medium, coupled with their large scale and “ad-hoc” nature raise some of the most important challenges for low-power wireless research over the next 5-10 years.

Through the involvement of team members in standardization activities, protocols and techniques are proposed for the standardization process with a view to becoming the *de-facto* standard for wireless industrial process automation. Besides producing top level research publications and standardization activities, EVA intends this activity to foster further collaborations with industrial partners.

4.2. Environmental Monitoring

Today, outdoor WSNs are used to monitor vast rural or semi-rural areas and may be used to detect fires. Another example is detecting fires in outdoor fuel depots, where the delivery of alarm messages to a monitoring station in an upper-bounded time is of prime importance. Other applications consist in monitoring the snow melting process in mountains, tracking the quality of water in cities, registering the height of water in pipes to foresee flooding, etc. These applications lead to a vast number of technical issues: deployment strategies to ensure suitable coverage and good network connectivity, energy efficiency, reliability and latency, etc.

We work on such applications in an associate team “REALMS” comprising members from EVA, the university of Berkeley and the university of Michigan.

4.3. The Internet of Things

The general agreement is that the Internet of Things (IoT) is composed of small, often battery-powered objects which measure and interact with the physical world, and encompasses smart home applications, wearables, smart city and smart plant applications.

It is absolutely essential to (1) clearly understand the limits and capabilities of the IoT, and (2) develop technologies which enable user expectation to be met.

The EVA team is dedicated to understanding and contributing to the IoT. In particular, the team maintains a good understanding of the different technologies at play (Bluetooth, IEEE 802.15.4, WiFi, cellular), and their trade-offs. Through scientific publications and other contributions, EVA helps establish which technology best fits which application.

⁰Highway Addressable Remote Transducer

4.4. Military, Energy and Aerospace

Through the HIPERCOM project, EVA has developed cutting-edge expertise in using wireless networks for military, energy and aerospace applications. Wireless networks are a key enabling technology in the application domains, as they allow physical processes to be instrumented (e.g. the structural health of an airplane) at a granularity not achievable by its wired counterpart. Using wireless technology in these domains does however raise many technical challenges, including end-to-end latency, energy-efficiency, reliability and Quality of Service (QoS). Mobility is often an additional constraint in energy and military applications. Achieving scalability is of paramount importance for tactical military networks, and, albeit to a lesser degree, for power plants. EVA will work in this domain.

Smart cities share the constraint of mobility (both pedestrian and vehicular) with tactical military networks. Vehicular Ad-hoc NETWORKS (VANETs) will play an important role in the development of smarter cities.

The coexistence of different networks operating in the same radio spectrum can cause interference that should be avoided. Cognitive radio provides secondary users with the frequency channels that are temporarily unused (or unassigned) by primary users. Such opportunistic behavior can also be applied to urban wireless sensor networks. Smart cities raise the problem of transmitting, gathering, processing and storing big data. Another issue is to provide the right information at the place where it is most needed.

4.5. Emergency Applications

In an “emergency” application, heterogeneous nodes of a wireless network cooperate to recover from a disruptive event in a timely fashion, thereby possibly saving human lives. These wireless networks can be rapidly deployed and are useful to assess damage and take initial decisions. Their primary goal is to maintain connectivity with the humans or mobile robots (possibly in a hostile environment) in charge of network deployment. The deployment should ensure the coverage of particular points or areas of interest. The wireless network has to cope with pedestrian mobility and robot/vehicle mobility. The environment, initially unknown, is progressively discovered and may contain numerous obstacles that should be avoided. The nodes of the wireless network are usually battery-powered. Since they are placed by a robot or a human, their weight is very limited. The protocols supported by these nodes should be energy-efficient to maximize network lifetime. In such a challenging environment, sensor nodes should be replaced before their batteries are depleted. It is therefore important to be able to accurately determine the battery lifetime of these nodes, enabling predictive maintenance.

4.6. Types of Wireless Networks

The EVA team will distinguish between opportunistic communication (which takes advantage of a favorable state) and collaborative communication (several entities collaborate to reach a common objective). Furthermore, determinism can be required to schedule medium access and node activity, and to predict energy consumption.

In the EVA project, we will propose **self-adaptive wireless networks** whose evolution is based on:

- optimization to minimize a single or multiple objective functions under some constraints (e.g. interference, or energy consumption in the routing process).
- machine learning to be able to predict a future state based on past states (e.g. link quality in a wireless sensor network) and to identify tendencies.

The types of wireless networks encountered in the application domains can be classified in the following categories.

4.6.1. Wireless Sensor and Mesh Networks

Standardization activities at the IETF have defined an “upper stack” allowing low-power mesh networks to be seamlessly integrated in the Internet (6LoWPAN), form multi-hop topologies (RPL), and interact with other devices like regular web servers (CoAP).

Major research challenges in sensor networks are mostly related to (predictable) power conservation and efficient multi-hop routing. Applications such as monitoring of mobile targets, and the generalization of smart phone devices and wearables, have introduced the need for WSN communication protocols to cope with node mobility and intermittent connectivity.

Extending WSN technology to new application spaces (e.g. security, sports, hostile environments) could also assist communication by seamless exchanges of information between individuals, between individuals and machines, or between machines, leading to the Internet of Things.

4.6.2. Deterministic Low-Power Networks

Wired sensor networks have been used for decades to automate production processes in industrial applications, through standards such as HART. Because of the unreliable nature of the wireless medium, a wireless version of such industrial networks was long considered infeasible.

In 2012, the publication of the IEEE 802.15.4e standard triggered a revolutionary trend in low-power mesh networking: merging the performance of industrial networks, with the ease-of-integration of IP-enabled networks. This integration process is spearheaded by the IETF 6TiSCH working group, created in 2013. A 6TiSCH network implements the IEEE 802.15.4e TSCH protocol, as well as IETF standards such as 6LoWPAN, RPL and CoAP. A 6TiSCH network is synchronized, and a communication schedule orchestrates all communication in the network. Deployments of pre-6TiSCH networks have shown that they can achieve over 99.999% end-to-end reliability, and a decade of battery lifetime.

The communication schedule of a 6TiSCH network can be built and maintained using a centralized, distributed, or hybrid scheduling approach. While the mechanisms for managing that schedule are being standardized by the IETF, which scheduling approach to use, and the associated limits in terms of reliability, throughput and power consumption remain entirely open research questions. Contributing to answering these questions is an important research direction for the EVA team.

4.6.3. MANETs and VANETs

In contrast to routing, other domains in MANETs such as medium access, multi-carrier transmission, quality of service, and quality of experience have received less attention. The establishment of research contracts for EVA in the field of MANETs is expected to remain substantial. MANETs will remain a key application domain for EVA with users such as the military, firefighters, emergency services and NGOs.

Vehicular Ad hoc Networks (VANETs) are arguably one of the most promising applications for MANETs. These networks primarily aim at improving road safety. Radio spectrum has been ring-fenced for VANETs worldwide, especially for safety applications. International standardization bodies are working on building efficient standards to govern vehicle-to-vehicle or vehicle-to-infrastructure communication.

4.6.4. Cellular and Device-to-Device Networks

We propose to initially focus this activity on spectrum sensing. For efficient spectrum sensing, the first step is to discover the links (sub-carriers) on which nodes may initiate communications. In Device-to-Device (D2D) networks, one difficulty is scalability.

For link sensing, we will study and design new random access schemes for D2D networks, starting from active signaling. This will assume the availability of a control channel devoted to D2D neighbor discovery. It is therefore naturally coupled with cognitive radio algorithms (allocating such resources): coordination of link discovery through eNode-B information exchanges can yield further spectrum usage optimization.

GANG Project-Team

4. Application Domains

4.1. Large scale networks

Application domains include evaluating Internet performances, the design of new peer-to-peer applications, enabling large scale networks, and developing tools for transportation networks.

GANG Project-Team

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MIMOVE Project-Team

4. Application Domains

4.1. Mobile urban systems for smarter cities

With the massive scale adoption of mobile devices and further expected significant growth in relation with the Internet of Things, mobile computing is impacting most – if not all – the ICT application domains. One such domain is the one of "smart cities". The smart city vision anticipates that the whole urban space, including buildings, power lines, gas lines, roadways, transport networks, and cell phones, can all be wired together and monitored. Detailed information about the functioning of the city then becomes available to both city dwellers and businesses, thus enabling better understanding and consequently management of the city's infrastructure and resources. This raises the prospect that cities will become more sustainable environments, ultimately enhancing the citizens' well being. There is the further promise of enabling radically new ways of living in, regulating, operating and managing cities, through the increasing active involvement of citizens by ways of crowd-sourcing/sensing and social networking.

Still, the vision of what smart cities should be about has been and keeps evolving at a fast pace in close concert with the latest technology trends. It is notably worth highlighting how mobile and social network use has reignited citizen engagement, thereby opening new perspectives for smart cities beyond data analytics that have been initially one of the core foci for smart cities technologies. Similarly, open data programs foster the engagement of citizens in the city operation and overall contribute to make our cities more sustainable. The unprecedented democratization of urban data fueled by open data channels, social networks and crowd sourcing enables not only the monitoring of the activities of the city but also the assessment of their nuisances based on their impact on the citizens, thereby prompting social and political actions. However, the comprehensive integration of urban data sources for the sake of sustainability remains largely unexplored. This is an application domain that we focus on, further leveraging our research on emergent mobile distributed systems, large-scale mobile sensing & actuation, and mobile social crowd-sensing.

In particular, we concentrate on the following specialized applications:

- **Democratization of urban data for healthy cities.** We integrate the various urban data sources, especially by way of crowd-Xing, to better understand city nuisances. This goes from raw pollution sensing (e.g., sensing noise) to the sensing of its impact on citizens (e.g., how people react to urban noise and how this affects their health).
- **Social applications.** Mobile applications are being considered by sociologists as a major vehicle to actively involve citizens and thereby prompt them to become activists. We study such a vehicle from the ICT perspective and in particular elicit relevant middleware solutions to ease the development of such "civic apps".

4.2. Home network diagnosis

With the availability of cheap broadband connectivity, Internet access from the home has become a ubiquity. Modern households host a multitude of networked devices, ranging from personal devices such as laptops and smartphones to printers and media centers. These devices connect among themselves and to the Internet via a local-area network—a home network—that has become an important part of the "Internet experience". In fact, ample anecdotal evidence suggests that the home network can cause a wide array of connectivity impediments, but their nature, prevalence, and significance remain largely unstudied.

Our long-term goal is to assist users with concrete indicators of the quality of their Internet access, causes of potential problems and—ideally—ways to fix them. We intend to develop a set of easy-to-use home network monitoring and diagnosis tools. The development of home network monitoring and diagnosis tools brings a number of challenges. First, home networks are heterogeneous. The set of devices, configurations, and applications in home networks vary significantly from one home to another. We must develop sophisticated techniques that can learn and adapt to any home network as well as to the level of expertise of the user. Second, Internet application and services are also heterogeneous with very diverse network requirements. We must develop methods that can infer application quality solely from the observation of (often encrypted) application network traffic. There are numerous ways in which applications can fail or experience poor performance in home networks. Often there are a number of explanations for a given symptom. We must devise techniques that can identify the most likely cause(s) for a given problem from a set of possible causes. Finally, even if we can identify the cause of the problem, we must then be able to identify a solution. It is important that the output of the diagnosis tools we build is “actionable”. Users should understand the output and know what to do.

In our partnership with Princeton University (associate team HOMENET) we have deployed monitoring infrastructure within users’ homes. We are developing a mostly passive measurement system to monitor the performance of user applications, which we call Network Microscope. We are developing Network Microscope to run in a box acting as home gateway. We have deployed these boxes in 50 homes in the US and 10 in France. The US deployment was ran and financed by the Wall Street Journal. They were interested in understanding the relationship between Internet access speed and video quality. We have been discussing with Internet regulators (in particular, FCC, ACERP, and BEREK) as well as residential access ISP in how Network Microscope can help overcome the shortcomings of existing Internet quality monitoring systems.

4.3. Mobile Internet quality of experience

Mobile Internet usage has boomed with the advent of ever smarter handheld devices and the spread of fast wireless access. People rely on mobile Internet for everyday tasks such as banking, shopping, or entertainment. The importance of mobile Internet in our lives raises people’s expectations. Ensuring good Internet user experience (or Quality of Experience—QoE) is challenging, due to the heavily distributed nature of Internet services. For mobile applications, this goal is even more challenging as access connectivity is less predictable due to user mobility, and the form factor of mobile devices limits the presentation of content. For these reasons, the ability to monitor QoE metrics of mobile applications is essential to determine when the perceived application quality degrades and what causes this degradation in the chain of delivery. Our goal is to improve QoE of mobile applications.

To achieve this goal, we are working on three main scientific objectives. First, we are working on novel methods to monitor mobile QoE. Within the IPL BetterNet we are developing the HostView for Android tool that runs directly on mobile devices to monitor network and system performance together with the user perception of performance. Second, we plan to develop models to predict QoE of mobile applications. We will leverage the datasets collected with HostView for Android to build data-driven models. Finally, our goal is to develop methods to optimize QoE for mobile users. We are currently developing optimization methods for interactive video applications. We envision users walking or driving by road-side WiFi access points (APs) with full 3G/LTE coverage and patchy WiFi coverage (i.e., community Wifi or Wifi APs on Lampposts) or devices with multiple 3G/LTE links. To achieve this goal, we plan to leverage multi-path and cross-layer optimizations.

4.4. Internet Scanning

Internet-wide scanning has enabled researchers to answer a wealth of new security and measurement questions ranging from “How are authoritarian regimes spying on journalists?” to “Are security notifications effective at prompting operators to patch?” Most of these studies have used tools like ZMap, which operates naively, scanning every IPv4 address once. This simplicity enables researchers to easily answer a question once, but the methodology scales poorly when continually scanning to detect changes, as networks change at dramatically

different rates. Service configurations change more frequently on cloud providers like Amazon and Azure than on residential networks. Internet providers in developing regions often have extremely short DHCP windows. Some networks are unstable with host presence varying wildly between different hours and others have distinct periodic patterns, e.g., hosts are only available during regional business hours. A handful of large autonomous systems have not had hosts present in decades. Our work in collaboration with Stanford University is developing more intelligent Internet-wide scanning methods to then implement a system that can scan continuously. Such a system will allow for up-to-date analysis of Internet trends and threats with real-time alerts of important events.

WHISPER Project-Team

4. Application Domains

4.1. Linux

Linux is an open-source operating system that is used in settings ranging from embedded systems to supercomputers. The most recent release of the Linux kernel, v4.14, comprises over 16 million lines of code, and supports 30 different families of CPU architectures, around 50 file systems, and thousands of device drivers. Linux is also in a rapid stage of development, with new versions being released roughly every 2.5 months. Recent versions have each incorporated around 13,500 commits, from around 1500 developers. These developers have a wide range of expertise, with some providing hundreds of patches per release, while others have contributed only one. Overall, the Linux kernel is critical software, but software in which the quality of the developed source code is highly variable. These features, combined with the fact that the Linux community is open to contributions and to the use of tools, make the Linux kernel an attractive target for software researchers. Tools that result from research can be directly integrated into the development of real software, where it can have a high, visible impact.

Starting from the work of Engler et al. [41], numerous research tools have been applied to the Linux kernel, typically for finding bugs [40], [57], [67], [76] or for computing software metrics [46], [78]. In our work, we have studied generic C bugs in Linux code [10], bugs in function protocol usage [51], [52], issues related to the processing of bug reports [71] and crash dumps [45], and the problem of backporting [66], [77], illustrating the variety of issues that can be explored on this code base. Unique among research groups working in this area, we have furthermore developed numerous contacts in the Linux developer community. These contacts provide insights into the problems actually faced by developers and serve as a means of validating the practical relevance of our work.

4.2. Device Drivers

Device drivers are essential to modern computing, to provide applications with access, via the operating system, to physical devices such as keyboards, disks, networks, and cameras. Development of new computing paradigms, such as the internet of things, is hampered because device driver development is challenging and error-prone, requiring a high level of expertise in both the targeted OS and the specific device. Furthermore, implementing just one driver is often not sufficient; today's computing landscape is characterized by a number of OSes, *e.g.*, Linux, Windows, MacOS, BSD and many real time OSes, and each is found in a wide range of variants and versions. All of these factors make the development, porting, backporting, and maintenance of device drivers a critical problem for device manufacturers, industry that requires specific devices, and even for ordinary users.

The last fifteen years have seen a number of approaches directed towards easing device driver development. Réveillère, who was supervised by G. Muller, proposes Devil [8], a domain-specific language for describing the low-level interface of a device. Chipounov *et al.* propose RevNic, [34] a template-based approach for porting device drivers from one OS to another. Ryzhyk *et al.* propose Termite, [68], [69] an approach for synthesizing device driver code from a specification of an OS and a device. Currently, these approaches have been successfully applied to only a small number of toy drivers. Indeed, Kadav and Swift [47] observe that these approaches make assumptions that are not satisfied by many drivers; for example, the assumption that a driver involves little computation other than the direct interaction between the OS and the device. At the same time, a number of tools have been developed for finding bugs in driver code. These tools include SDV [25], Coverity [41], CP-Miner, [56] PR-Miner [57], and Coccinelle [9]. These approaches, however, focus on analyzing existing code, and do not provide guidelines on structuring drivers.

In summary, there is still a need for a methodology that first helps the developer understand the software architecture of drivers for commonly used operating systems, and then provides tools for the maintenance of existing drivers.

ALMANACH Project-Team

4. Application Domains

4.1. Application domains for ALMAnaCH

ALMAnaCH's research areas cover Natural Language Processing (nowadays identified as a sub-domain of Artificial Intelligence) and Digital Humanities. Application domains are therefore numerous, as witnessed by ALMAnaCH's multiple academic and industrial collaborations, for which see the relevant sections. Examples of application domains for NLP include:

- Information extraction, information retrieval, text mining (ex.: opinion surveys)
- Text generation, text simplification, automatic summarisation
- Spelling correction (writing aid, post-OCR, normalisation of noisy/non-canonical texts)
- Machine translation, computer-aided translation
- Chatbots, conversational agents, question answering systems
- Medical applications (early diagnosis, language-based medical monitoring...)
- Applications in linguistics (modelling languages and their evolution, sociolinguistic studies...)
- Digital humanities (exploitation of text documents, for instance in historical research)

COML Team

4. Application Domains

4.1. Speech processing for underresourced languages

We plan to apply our algorithms for the unsupervised discovery of speech units to problems relevant to language documentation and the construction of speech processing pipelines for underresourced languages.

4.2. Tools for the analysis of naturalistic speech corpora

Daylong recordings of speech in the wild gives rise a to number of specific analysis difficulties. We plan to use our expertise in speech processing to develop tools for performing signal processing and helping annotation of such resources for the purpose of phonetic or linguistic analysis.

RITS Project-Team

4. Application Domains

4.1. Introduction

While the preceding section focused on methodology, in connection with automated guided vehicles, it should be stressed that the evolution of the problems which we deal with remains often guided by the technological developments. We enumerate three fields of application whose relative importance varies with time and which have strong mutual dependencies: driving assistance, cars available in self-service mode and fully automated vehicles (cybercars).

4.2. Driving assistance

Several techniques will soon help drivers. One of the first immediate goal is to improve security by alerting the driver when some potentially dangerous or dangerous situations arise, i.e. collision warning systems or lane tracking could help a bus driver and surrounding vehicle drivers to more efficiently operate their vehicles. Human factors issues could be addressed to control the driver workload based on additional information processing requirements. Another issue is to optimize individual journeys. This means developing software for calculating optimal (for the user or for the community) paths. Nowadays, path planning software is based on a static view of the traffic: efforts have to be done to take the dynamic component in account.

4.3. New transportation systems

The problems related to the abusive use of the individual car in large cities led the populations and the political leaders to support the development of public transport. A demand exists for a transport of people and goods which associates quality of service, environmental protection and access to the greatest number. Thus the tram and the light subways of VAL type recently introduced into several cities in France conquered the populations, in spite of high financial costs. However, these means of mass transportation are only possible on lines on which there is a keen demand. As soon as one moves away from these “lines of desire” or when one deviates from the rush hours, these modes become expensive and offer can thus only be limited in space and time. To give a more flexible offer, it is necessary to plan more individual modes which approach the car as we know it. However, if one wants to enjoy the benefits of the individual car without suffering from their disadvantages, it is necessary to try to match several criteria: availability anywhere and anytime to all, lower air and soils pollution as well as sound levels, reduced ground space occupation, security, low cost. Electric or gas vehicles available in self-service, as in the Praxitèle system, bring a first response to these criteria. To be able to still better meet the needs, it is however necessary to re-examine the design of the vehicles on the following points:

- ease empty car moves to better distribute them;
- better use of information systems inboard and on ground;
- better integrate this system in the global transportation system.

These systems are now operating. The challenge is to bring them to an industrial phase by transferring technologies to these still experimental projects.

4.4. Automated vehicles

The long term effort of the project is to put automatically guided vehicles (cybercars) on the road. It seems too early to mix cybercars and traditional vehicles, but data processing and automation now make it possible to consider in the relatively short term the development of such vehicles and the adapted infrastructures. RITS aims at using these technologies on experimental platforms (vehicles and infrastructures) to accelerate the technology transfer and to innovate in this field. Other application can be precision docking systems that will allow buses to be automatically maneuvered into a loading zone or maintenance area, allowing easier access for passengers, or more efficient maintenance operations. Transit operating costs will also be reduced through decreased maintenance costs and less damage to the braking and steering systems. Regarding technical topics, several aspects of Cybercars have been developed at RITS this year. First, we have stabilized a generic Cycab architecture involving Inria SynDEx tool and CAN communications. The critical part of the vehicle is using a real-time SynDEx application controlling the actuators via two Motorola's MPC555. Today, we have decided to migrate to the new dsPIC architecture for more efficiency and ease of use. This application has a second feature, it can receive commands from an external source (Asynchronously to this time) on a second CAN bus. This external source can be a PC or a dedicated CPU, we call it high level. To work on the high level, in the past years we have been developing a R&D framework called (Taxi) which used to take control of the vehicle (Cycab and Yamaha) and process data such as gyro, GPS, cameras, wireless communications and so on. In order to rely on a professional and maintained solution, we use the RTMaps SDK development platform for our developments and demonstrations. These demonstrations include: reliable SLAMMOT algorithm using 2 to 4 laser sensors simultaneously, automatic line/road following techniques, PDA remote control, multi sensors data fusion, collaborative perception via ad-hoc network. The second main topic is inter-vehicle communications using ad-hoc networks. We have worked with the EVA team for setting and tuning OLSR, a dynamic routing protocol for vehicles communications. Our goal is to develop a vehicle dedicated communication software suite, running on a specialized hardware. It can be linked also with the Taxi Framework for getting data such GPS information's to help the routing algorithm.

VALDA Project-Team

4. Application Domains

4.1. Personal Information Management Systems

We recall that Valda's focus is on human-centric data, i.e., data produced by humans, explicitly or implicitly, or more generally containing information about humans. Quite naturally, we have used as a privileged application area to validate Valda's results that of personal information management systems (Pims for short) [33].

A Pims is a system that allows a user to integrate her own data, e.g., emails and other kinds of messages, calendar, contacts, web search, social network, travel information, work projects, etc. Such information is commonly spread across different services. The goal is to give back to a user the control on her information, allowing her to formulate queries such as "What kind of interaction did I have recently with Alice B.?", "Where were my last ten business trips, and who helped me plan them?". The system has to orchestrate queries to the various services (which means knowing the existence of these services, and how to interact with them), integrate information from them (which means having data models for this information and its representation in the services), e.g., align a GPS location of the user to a business address or place mentioned in an email, or an event in a calendar to some event in a Web search. This information must be accessed intensionally: for instance, costly information extraction tools should only be run on emails which seem relevant, perhaps identified by a less costly cursory analysis (this means, in turn, obtaining a cost model for access to the different services). Impacted people can be found by examining events in the user's calendar and determining who is likely to attend them, perhaps based on email exchanges or former events' participant lists. Of course, uncertainty has to be maintained along the entire process, and provenance information is needed to explain query results to the user (e.g., indicate which meetings and trips are relevant to each person of the output). Knowledge about services, their data models, their costs, need either to be provided by the system designer, or to be automatically learned from interaction with these services, as in [68].

One motivation for that choice is that Pims concentrate many of the problems we intend to investigate: heterogeneity (various sources, each with a different structure), massive distribution (information spread out over the Web, in numerous sources), rapid evolution (new data regularly added), intensionality (knowledge from Wikidata, OpenStreetMap...), confidentiality and security (mostly private data), and uncertainty (very variable quality). Though the data is distributed, its size is relatively modest; other applications may be considered for works focusing on processing data at large scale, which is a potential research direction within Valda, though not our main focus. Another strong motivation for the choice of Pims as application domain is the importance of this application from a societal viewpoint.

A Pims is essentially a system built on top of a user's *personal knowledge base*; such knowledge bases are reminiscent of those found in the Semantic Web, e.g., linked open data. Some issues, such as ontology alignment [71] exist in both scenarios. However, there are some fundamental differences in building personal knowledge bases vs collecting information from the Semantic Web: first, the scope is quite smaller, as one is only interested in knowledge related to a given individual; second, a small proportion of the data is already present in the form of semantic information, most needs to be extracted and annotated through appropriate wrappers and enrichers; third, though the linked open data is meant to be read-only, the only update possible to a user being adding new triples, a personal knowledge base is very much something that a user needs to be able to edit, and propagating updates from the knowledge base to original data sources is a challenge in itself.

4.2. Web Data

The choice of Pims is not exclusive. We also consider other application areas as well. In particular, we have worked in the past and have a strong expertise on Web data [38] in a broad sense: semi-structured, structured, or unstructured content extracted from Web databases [68]; knowledge bases from the Semantic Web [71];

social networks [66]; Web archives and Web crawls [54]; Web applications and deep Web databases [47]; crowdsourcing platforms [41]. We intend to continue using Web data as a natural application domain for the research within Valda when relevant. For instance [45], deep Web databases are a natural application scenario for intensional data management issues: determining if a deep Web database contains some information requires optimizing the number of costly requests to that database.

A common aspect of both personal information and Web data is that their exploitation raises ethical considerations. Thus, a user needs to remain fully in control of the usage that is made of her personal information; a search engine or recommender system that ranks Web content for display to a specific user needs to do so in an unbiased, justifiable, manner. These ethical constraints sometimes forbid some technically solutions that may be technically useful, such as sharing a model learned from the personal data of a user to another user, or using blackboxes to rank query result. We fully intend to consider these ethical considerations within Valda. One of the main goals of a Pims is indeed to empower the user with a full control on the use of this data.

WILLOW Team

4. Application Domains

4.1. Introduction

We believe that foundational modeling work should be grounded in applications. This includes (but is not restricted to) the following high-impact domains.

4.2. Quantitative image analysis in science and humanities

We plan to apply our 3D object and scene modeling and analysis technology to image-based modeling of human skeletons and artifacts in anthropology, and large-scale site indexing, modeling, and retrieval in archaeology and cultural heritage preservation. Most existing work in this domain concentrates on image-based rendering, that is, the synthesis of good-looking pictures of artifacts and digs. We plan to focus instead on quantitative applications. We are engaged in a project involving the archaeology laboratory at ENS and focusing on image-based artifact modeling and decorative pattern retrieval in Pompeii. Application of our 3D reconstruction technology is now being explored in the field of cultural heritage and archeology by the start-up Iconem, founded by Y. Ubelmann, a Willow collaborator.

4.3. Video Annotation, Interpretation, and Retrieval

Both specific and category-level object and scene recognition can be used to annotate, augment, index, and retrieve video segments in the audiovisual domain. The Video Google system developed by Sivic and Zisserman (2005) for retrieving shots containing specific objects is an early success in that area. A sample application, suggested by discussions with Institut National de l'Audiovisuel (INA) staff, is to match set photographs with actual shots in film and video archives, despite the fact that detailed timetables and/or annotations are typically not available for either medium. Automatically annotating the shots is of course also relevant for archives that may record hundreds of thousands of hours of video. Some of these applications will be pursued in our MSR-Inria project.