RESEARCH CENTER

FIELD
Digital Health, Biology and Earth

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Section Application Domains

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BIGS Project-Team

4. Application Domains

4.1. Tumor growth

Cancer is the result of inter-dependent multi-scale phenomena and this is mainly why the understanding of its spread is still an unsolved problem. In integrative biology, mathematical models play a central role; they help biologists and clinicians to answer complex questions through numerical simulations and statistical analyses. The main issue here is to better understand and describe the role of cell damage heterogeneity and associated mutant cell phenotypes in the therapeutic responses of cancer cell populations submitted to a radiotherapy sessions during *in vitro* experiments. The cell heterogeneity is often described as randomness in mathematical modeling and different representations, such as Markov chains, branching processes and even stochastic differential equations, have been recently used.

4.2. Photodynamic therapy

Since 1988, some control system scientists and biologists at the CRAN [0] have worked together to develop the photodynamic therapy (PDT in the sequel), an alternative treatment for cancer, by means of a model-based approach. The global aim in this direction is to use statistical as well as mechanistic models in order to improve the response reproducibility, help biologists and chemists in the design of new photosensitizing agents and provide insight into complex phenomena associated with oncogenesis, tumor angiogenesis and interactions with the treatment. This heavily relies on the production of accurate and simple enough models involving various type of stochastic processes, such as Markov chains, branching processes and stochastic differential equations. The main questions here concern generally identification or estimation properties, but simulation issues can be important too.

4.3. Genomic data and micro-organisms population study

Generation genomic technologies allow clinicians and biomedical researchers to drastically increase the amount of genomic data collected on large cohort of patients and populations. We want to contribute to a better understanding of the correlations between gene trough their expression data, of the structure of ARN and of the genetic bases of drug response and disease and to detect significant sequences characterizing a gene. For instance the biopharmaceutical company Transgene has recently contacted us to analyse their genomic and proteomic data particularly for the purpose to find markers of the success of therapies that they develop against cancer.

Network inference has also applications for the analysis of micro-organisms population, that we apply to micro-organism inside and around the truffle trough a collaboration with INRA Nancy. We want also study other specific complex microbial communities like that found at tree roots in order to characterize phenotype of the tree. There is also application in human health (for instance identification of network between bacteria inside colon).

4.4. Epidemiology and e-health

Trough J.-M. Monnez and his collaborator Pr E. Albuisson, BIGS is stakeholder of projects with University Hospital of Nancy that is FHU CARTAGE (Fédération Hospitalo Universitaire Cardial and ARTerial AGEing; leader: Pr Athanase BENETOS), RHU Fight HF (Fighting Heart Failure; leader: Pr Patrick ROSSIGNOL), and "Handle your heart", team responsible for the creation of a drug prescription support software for the treatment of heart failure. All these projects are in the context of personalized medicine and deal with biomarkers research; prognostic value of quantitative variables and events and scoring of heart failure. Other collaborations with clinicians concern foetopathology and cancer again.

[0] Centre de Recherche en Automatique de Nancy, http://www.cran.uhp-nancy.fr/francais/themes_rech/sbs/beam/index.php

4.5. Dynamics of telomeres

A telomere is a region of repetitive and non coding nucleotide sequences at each end of a chromosome. The telomeres are disposable buffers at the ends of chromosomes which are truncated during cell division; so that, over time, due to each cell division, the telomere ends become shorter. By this way, they are markers of aging. Mathematical modeling of telomere dynamics is recent [36], [107], [91], [49]. Trough a collaboration with Pr A. Benetos, geriatrician at CHU Nancy, and some members of Inria team TOSCA, we want to work in three connected directions: (1) propose a dynamical model for the lengths of telomeres and study its mathematical properties (long term behavior of the distribution of lengths, quasi-stationarity, etc); (2) use these properties to develop new statistical methods for estimating the various parameters; and (3) find and use a suitable methodology for the analysis of the available data (Pr Benetos) for instance for the study of the length distribution for a subject and its evolution.

BONSAI Project-Team

4. Application Domains

4.1. Life Sciences and health

Our research plays a pivotal role in all fields of life sciences and health where genomic data are involved. This includes more specifically the following topics: plant genomics (genome structure, evolution, microRNAs), cancer (leukemia, mosaic tumors), drug design (NRPSs), environment (metagenomics and metatranscriptomics), virology (evolution, RNA structures) ...

CAPSID Project-Team

4. Application Domains

4.1. Biomedical Knowledge Discovery

Participants: Marie-Dominique Devignes [contact person], Sabeur Aridhi, David Ritchie.

This projects in this domain are carried out in collaboration with the Orpailleur Team.

Huge and ever increasing amounts of biomedical data ("Big Data") are bringing new challenges and novel opportunities for knowledge discovery in biomedicine. We are actively collaborating with biologists and clinicians to design and implement approaches for selecting, integrating, and mining biomedical data in various areas. In particular, we are focusing on leveraging bio-ontologies at all steps of this process (the main thesis topic of Gabin Personeni, co-supervised by Marie-Dominique Devignes and Adrien Coulet from the Orpailleur team). One specific application concerns exploiting Linked Open Data (LOD) to characterise the genes responsible for intellectual deficiency. This work is in collaboration with Pr. P. Jonveaux of the Laboratoire de Génétique Humaine at CHRU Nancy [56], [57]. This involves using inductive logic programming as a machine learning method and at least three different ontologies (Gene Ontology, Human Phenotype Ontology, and Disease Ontology).

Recently, a new application for biomedical knowledge discovery has emerged from the ANR "FIGHT-HF" (fight heart failure) project, which is in collaboration with several INSERM teams at CHRU Nancy. In this case, the molecular mechanisms that underly HF at the cellular and tissue levels will be considered against a background of all available data and ontologies, and represented in a single integrated complex network. A network platform is under construction with the help of a young start-up company called Edgeleap. Together with this company, we are developing query and analysis facilities to help biologists and clinicians to identify relevant biomarkers for patient phenotyping [25]. Docking of small molecules on candidate receptors, as well as protein-protein docking will also be used to clarify a certain number of relations in the complex HF network.

4.2. Prokaryotic Type IV Secretion Systems

Participants: Marie-Dominique Devignes [contact person], Bernard Maigret, Isaure Chauvot de Beauchêne, David Ritchie.

Prokaryotic type IV secretion systems constitute a fascinating example of a family of nanomachines capable of translocating DNA and protein molecules through the cell membrane from one cell to another [30]. The complete system involves at least 12 proteins. The structure of the core channel involving three of these proteins has recently been determined by cryo-EM experiments [41], [63]. However, the detailed nature of the interactions between the remaining components and those of the core channel remains to be resolved. Therefore, these secretion systems represent another family of complex biological systems (scales 2 and 3) that call for integrated modeling approaches to fully understand their machinery.

In the frame of the "MBI" platform (see Section 6.8), MD Devignes is pursuing her collaboration with Nathalie Leblond of the Genome Dynamics and Microbial Adaptation (DynAMic) laboratory (UMR 1128, Université de Lorraine, INRA) on the discovery of new integrative conjugative elements (ICEs) and integrative mobilisable elements (IMEs) in prokaryotic genomes. These elements use Type IV secretion systems for transferring DNA horizontally from one cell to another. We have discovered more than 200 new ICEs/IMEs by systematic exploration of 72 Streptococcus genome. As these elements encode all or a subset of the components of the Type IV secretion system, they constitute a valuable source of sequence data and constraints for modeling these systems in 3D. Another interesting aspect of this particular system is that unlike other secretion systems, the Type IV secretion systems are not restricted to a particular group of bacteria.

4.3. G-protein Coupled Receptors

Participants: Bernard Maigret [contact person], David Ritchie, Vincent Leroux.

G-protein coupled receptors (GPCRs) are cell surface proteins which detect chemical signals outside a cell and which transform these signals into a cascade of cellular changes. Historically, the most well documented signaling cascade is the one driven by G-proteins trimers (guanine nucleotide binding proteins) [43] which ultimately regulate many cellular processes such as transcription, enzyme activity, and homeostatis, for example. But other pathways have recently been associated with the signals triggered by GPCRs, involving other proteins such as arrestins and kinases which drive other important cellular activities. For example, β-arrestin activation can block GPCR-mediated apoptosis (cell death). Malfunctions in such processes are related to diseases such as diabetes, neurological disorders, cardiovascular disease, and cancer. Thus, GPCRs are one of the main protein families targeted by therapeutic drugs [38] and the focus of much bio-medical research. Indeed, approximately 40–50% of current therapeutic molecules target GPCRs. However, despite enormous efforts, the main difficulty here is the lack of experimentally solved 3D structures for most GPCRs. Hence, computational modeling tools are widely recognized as necessary to help understand GPCR functioning and thus biomedical innovation and drug design.

In collaboration with the BIOS team (INRA Tours) and the AMIB team (Inria Saclay – Île de France) we used our Hex protein docking software to help model a multi-component G-protein coupled receptor (GPCR) complex [35]. The resulting 3D structure was shown to be consistent with the known experimental data for the protein components of this trans-membrane molecular signaling system. As part of an on-going collaboration with the Centre for Interdisciplinary Research (CIRB) at Collège de France, we modeled the interaction between the Apelin peptide and a GPCR called ApelinR [42]. This study provided mechanistic insights which could lead to the development of therapeutic agents for the treatment of heart failure.

DYLISS Project-Team

4. Application Domains

4.1. Application domain in bioinformatics

As mentioned before, our main goal in biology is to characterize groups of genetic actors that control the response of living species capable of facing extreme environments. To focus our developments, applications and collaborations, we have identified three biological questions which deserve integrative studies. Each axis may be considered independently from the others although their combination, a mid-term challenge, will have the best impact in practice towards the long-term perspective of identifying proteins controlling the production of a metabolite of industrial interest. It is illustrated in our presentation for a major algae product: polyunsaturated fatty acids (PUFAs) and their derivatives.

Integrative biology with combinatorial optimization. The first axis of the project (data integration) aims at identifying *who* is involved in the specific response of a biological system to an environmental stress. Targeted actors will mainly consist in groups of genetic products or biological pathways. For instance, which pathways are involved in the specific production of PUFAs in brown algae? The main work is to represent in a system of logical constraints the full knowledge at hand concerning the genetic or metabolic actors, the available observations and the effects of the system dynamics. To this aim, we focus on the use of Answer Set Programming as we are experienced in modeling with this paradigm and we have a strong partnership with a computer science team leader in the development of dedicated grounders and solvers (Potsdam university). See Sec. 3.1 .

Systems biology with discrete dynamical modeling. Once a model is built and its main actors are identified, the next step is to clarify *how* they combine to control the system. This is the second axis of the project. Roughly, the fine tuning of the system response may be of two types. Either it results from the discrete combinatorics of the actors, as the result of a genetic adaptation to extreme environmental conditions or the difference between species is rather at the enzyme-efficiency level. For instance, if PUFAs are found to be produced using a set of pathways specific to brown algae, our work on dynamical modeling will consist to apply constraint-based combinatorial approaches to select consistent combinations of pathways controlling the metabolite production. Otherwise, if enzymes controlling the production of PUFAs are found to be expressed in other algaes, it suggests that the response of the system is rather governed by a fine quantitative tuning of pathways. In this case, we use symbolic dynamics and average-case analysis of algorithms to weight the respective importance of interactions in observed phenotypes (see Sec. 3.2 and Fig. 2). This specific approach is motivated by the quite restricted spectrum of available physiological observations over the asymptotic dynamics of the biological system.

Biological sequence annotation with grammatical inference and modelling In order to check the accuracy of in-silico predictions, a third research axis of the team is to extract genetic actors responsible of biological pathways of interest in the targeted organism and locate them in the genome. In our guiding example, active proteins implied in PUFAs controlling pathways have to be precisely identified. Actors structures are represented by syntactic models (see Fig. 3). We use knowledge-based induction on far instances for the recognition of new members of a given sequence family within non-model genomes (see Fig. 3). A main objective is to model enzyme specificity with highly expressive syntactic structures - context-free model - in order to take into account constraints imposed by local domains or long-distance interactions within a protein sequence. See Sec. 3.3 for details.

Data classification with data sciences All the methods presented in the previous section usually result in pools of candidates which equivalently explain the data and knowlegde. These candidates can by dynamical systems, compounds, biological sequences, proteins... In any case, the output of our formal methods generally deserves a a-posteriori investigation and filtering. To that goal, we rely on two classes of symbolic technics: semantic web technologies and Formal Concept Analysis See Sec. 3.4 for details.

4.2. Application fields in biology

Our methods are applied in several fields of molecular biology.

Our main application field is **marine biology**, as it is a transversal field with respect to issues in integrative biology, dynamical systems and sequence analysis. Our main collaborators work at the Station Biologique de Roscoff. We are strongly involved in the study of brown algae: the *meneco, memap and memerge* tools were designed to realize a complete reconstruction of metabolic networks for non-benchmark species [82], [68]. On the same application model, the pattern discovery tool *protomata learner* combined with supervised bi-clustering based on formal concept analysis allows for the classification of sub-families of specific proteins [65]. The same tool also allowed us to gain a better understanding of cyanobacteria proteins [3]. At the larger level of 4D structures, classification technics have also allowed us to introduce new methods for the characterization of viruses in marine metagenomic sample [19]. Finally, in dynamical systems, we use asymptotic analysis (tool *pogg*) to decipher the initiation of sea urchin translation [55] [24]. We are currently involved in two new applications in this domain: the team participates to a Inria Project Lab program with the Biocore and Ange Inria teams, focused on the understanding on green micro-algae; and we are involved in the deciphering of phytoplancton variability at the system biology level in collaboration with the Station Biologique de Roscoff (ANR Samosa).

In **micro-biology**, our main issue is the understanding of bacteria living in extreme environments, mainly in collaboration with the group of bioinformatics at Universidad de Chile (funded by CMM, CRG and Inria-Chile). In order to elucidate the main characteristics of these bacteria, we develop efficient methods to identify the main groups of regulators for their specific response in their living environment. To that purpose, we use constraints-based modeling and combinatorial optimization. The integrative biology tools *meneco bioquali, ingranalysis, shogen, lombarde* were designed in this context [6]. in 2016, two applications focused on the study of extremophile consortium of bacteria have been performed with these tools [15], [13]. In parallel, in collaboration with Ifremer (Brest), we have conducted similar work to decipher protein-protein interactions within archebacteria [81]. Our sequence analysis tool (*logol*) allowed us to build and maintain a very expressive CRISPR database [10] [54].

Similarly, in **agriculture**, our goal is to propose methods to identify regulators of very complex phenotypes related to environmental issues. In collaboration with researchers from Inra/Pegase and Inra/Igeep laboratories, we develop methods to distinguish the response of breeding animals to different diaries or treatments [47] and characterize upstream transcriptional regulators [61], with applications in porks [70], [71] [20]. The pattern matching tool *logol* also allows for a fine identification of transcription factor motifs applied to chicken [67] [54]. Semantic-based analysis was useful for interpreting differences of gene expression in pork meat [72]. Finally, Constraints-based programming also allows us to decipher regulators of reproduction for pea aphids [75], [98] and paved the way to the recent research track initiated in the team about integration of heterogeneous data with RDF-technologies (see askomics software) [37], [45].

Similarly, in **agriculture**, our goal is to propose methods to identify regulators of very complex phenotypes related to environmental issues. In collaboration with researchers from Inra/Pegase laboratory, we develop methods to distinguish the response of breeding animals to different diaries or treatments [47] and characterize upstream transcriptional regulators [61], applied to porks [70], [71] [20]. The pattern matching tool *logol* also allows for a fine identification of transcription factor motifs applied to chicken [67] [54]. Semantic-based analysis was useful for interpreting differences of gene expression in pork meat [72].

In addition, constraints-based programming also allows us to decipher regulators of reproduction for the pea aphid, an insect that is a pest on plants [75], [98]. This was performed in collaboration with Inra/Igepp . This paved the way to the recent research track initiated in the team about integration of heterogeneous data with RDF-technologies (see askomics software) [37], [45] and about graph-compression (see powergrasp software).

In **bio-medical applications**, we focus our attention on the confrontation of large-scale measurements with large-scale knowledge repositories about regulation pathways such as Transpath, PID or pathway commons. In collaboration with Institut Curie, we have studied the Ewing Sarcoma regulation network to test the capability of our tool *bioquali* to accurately correct and predict a large-scale network behavior [51]. Our ongoing studies

in this field focus on the exhaustive learning of discrete dynamical networks matching with experimental data, as a case study for modeling experimental design with constraints-based approaches. To that purpose, we collaborate with J. Saez Rodriguez group at EBI [94] and N. Theret group at Inserm/Irset (Rennes) [49]. The dynamical system tools *caspo and cadbiom* were designed within these collaborations. Ongoing studies focus on the understanding of the metabolism of xenobiotics (mecagenotox program) and the filtering of sets of regulatory compounds within large-scale signaling network (TGFSysBio project).

ERABLE Project-Team

4. Application Domains

4.1. Biology

The main area of application of ERABLE is biology understood in its more general sense, with a special focus on symbiosis and on intracellular interactions.

GENSCALE Project-Team

4. Application Domains

4.1. Introduction

Today, sequencing data are intensively used in many life science projects. The methodologies developed by the GenScale group are generic approaches that can be applied to a large panel of domains such as health, agronomy or environment areas. The next sections briefly describe examples of our activity in these different domains.

4.2. Health

Cancer diagnostic: from a pool of known genes, the aim is to detect potential mutations that perturb the activity of these genes. Pointing out the right gene helps in prescribing the right drug. The bioinformatics analysis is based on the detection of SNPs (Single Nucleotide Polymorphism) from a set of target genes.

Microbiology: Streptococcus bacteria are considered as major pathogens for humans and lead to many infections. The cause of their pathogenicity can be studied from their genomic structure by comparing different strains. Text of the genomes must first be constructed (assembly process) before to be analyzed (comparative genomic).

HLA genotyping: The human leukocyte antigen (HLA) system drives the regulation of the human immune system. The HLA genes reside on chromosome 6 and have a large number of alleles. Genotyping this group of genes can be done by a deep sequencing of the HLA region, and by comparing reads with a HLA databank (intensive sequence comparison).

4.3. Agronomy and Environment

Improving plant breeding: such projects aim at 1) identifying favorable alleles at loci contributing to phenotypic variation, 2) characterizing N-traits at the functional level and 3) providing robust multi-locus SNP-based predictors of the breeding value of agronomical traits under polygenic control. Underlying bioinformatics processing is the detection of informative zones (QTL) on the plant genomes.

Insect study: Insects represent major crop pests, justifying the need for control strategies to limit population outbreaks and the dissemination of plant viruses they frequently transmit. Several issues are investigated through the analysis and comparison of their genomes: understanding their phenotypic plasticity such as their reproduction mode changes, identifying the genomic sources of adaptation to their host plant and of ecological speciation, and understanding the relationships with their bacterial symbiotic communities.

Ocean biodiversity: The metagenomic analysis of seawater samples provides an original way to study the ecosystems of the oceans. Through the biodiversity analysis of different ocean spots, many biological questions can be addressed, such as the plankton biodiversity and their role, for example, in the CO2 sequestration.

IBIS Project-Team (section vide)

LIFEWARE Project-Team

4. Application Domains

4.1. Preamble

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

4.2. Modeling platform for systems biology

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

4.3. Couplings between the cell cycle and the circadian clock

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

4.4. Biosensor design and implementation in non-living protocells

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

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

MORPHEME Project-Team (section vide)

PLEIADE Team

4. Application Domains

4.1. Genome and transcriptome annotation, to model function

Sequencing genomes and transcriptomes provides a picture of how a biological system can function, or does function under a given physiological condition. Simultaneous sequencing of a group of related organisms is now a routine procedure in biological laboratories for studying a behavior of interest, and provides a marvelous opportunity for building a comprehensive knowledge base of the relations between genomes. Key elements in mining these relations are: classifying the genes in related organisms and the reactions in their metabolic networks, recognizing the patterns that describe shared features, and highlighting specific differences.

PLEIADE will develops applications in comparative genomics of related organisms, using new mathematical tools for representing compactly, at different scales of difference, comparisons between related genomes. New methods based on computational geometry refine these comparisons. Compact representations can be stored, exchanged, and combined. They will form the basis of new simultaneous genome annotation methods, linked directly to abductive inference methods for building functional models of the organisms and their communities.

Our ambition in biotechnology is to permit the design of synthetic or genetically selected organisms at an abstract level, and guide the modification or assembly of a new genome. Our effort is focused on two main applications: genetic engineering and synthetic biology of oil-producing organisms (biofuels in CAER, palm oils), and improving and selecting starter microorganisms used in winemaking (collaboration with the ISVV and the BioLaffort company).

4.2. Molecular based systematics and taxonomy

Defining and recognizing myriads of species in biosphere has taken phenomenal energy over the past centuries and remains a major goal of Natural History. It is an iconic paradigm in pattern recognition (clustering has coevolved with numerical taxonomy many decades ago). Developments in evolution and molecular biology, as well as in data analysis, have over the past decades enabled a profound revolution, where species can be delimited and recognized by data analysis of sequences. We aim at proposing new tools, in the framework of E-science, which make possible (i) better exploration of the diversity in a given clade, and (ii) assignment of a place in these patterns for new, unknown organisms, using information provided by sets of sequences. This will require investment in data analysis, machine learning, and pattern recognition to deal with the volumes of data and their complexity.

One example of this project is about the diversity of trees in Amazonian forest, in collaboration with botanists in French Guiana. Protists (unicellular Eukaryots) are by far more diverse than plants, and far less known. Molecular exploration of Eukaryotes diversity is nowadays a standard in biodiversity studies. Data are available, through metagenomics, as an avalanche and make molecular diversity enter the domain of Big Data. Hence, an effort will be invested, in collaboration with other Inria teams (GenScale, HiePACS) for porting to HPC algorithms of pattern recognition and machine learning, or distance geometry, for these tools to be available as well in metagenomics. This will be developed first on diatoms (unicellular algae) in collaboration with INRA team at Thonon and University of Uppsala), on pathogens of tomato and grapewine, within an existing network, and on bacterial communities, in collaboration with University of Pau. For the latter, the studies will extend to correlations between molecular diversity and sets of traits and functions in the ecosystem.

4.3. Community ecology and population genetics

Community assembly models how species can assemble or diassemble to build stable or metastable communities. It has grown out of inventories of countable organisms. Using *metagenomics* one can produce molecular based inventories at rates never reached before. Most communities can be understood as pathways of carbon exchange, mostly in the form of sugar, between species. Even a plant cannot exist without carbon exchange with its rhizosphere. Two main routes for carbon exchange have been recognized: predation and parasitism. In predation, interactions–even if sometimes dramatic–may be loose and infrequent, whereas parasitism requires what Claude Combes has called intimate and sustainable interactions [22]. About one decade ago, some works [30] have proposed a comprehensive framework to link the studies of biodiversity with community assembly. This is still incipient research, connecting community ecology and biogeography.

We aim at developping graph-based models of co-occurence between species from NGS inventories in metagenomics, i.e. recognition of patterns in community assembly, and as a further layer to study links, if any, between diversity at different scales and community assemblies, starting from current, but oversimplified theories, where species assemble from a regional pool either randomly, as in neutral models, or by environmental filtering, as in niche modeling. We propose to study community assembly as a multiscale process between nested pools, both in tree communities in Amazonia, and diatom communities in freshwaters. This will be a step towards community genomics, which adds an ecological flavour to metagenomics.

Convergence between the processes that shape genetic diversity and community diversity–drift, selection, mutation/speciation and migration–has been noted for decades and is now a paradigm, establishing a continuous scale between levels of diversity patterns, beyond classical approaches based on iconic levels like species and populations. We will aim at deciphering diversity pattern along these gradients, connecting population and community genetics. Therefore, some key points must be adressed on reliability of tools.

Next-generation sequencing technologies are now an essential tool in population and community genomics, either for making evolutionary inferences or for developing SNPs for population genotyping analyses. Two problems are highlighted in the literature related to the use of those technologies for population genomics: variable sequence coverage and higher sequencing error in comparison to the Sanger sequencing technology. Methods are developed to develop unbiased estimates of key parameters, especially integrating sequencing errors [28]. An additional problem can be created when sequences are mapped on a reference sequence, either the sequenced species or an heterologous one, since paralogous genes are then considered to be the same physical position, creating a false signal of diversity [25]. Several approaches were proposed to correct for paralogy, either by working directly on the sequences issued from mapped reads [25] or by filtering detected SNPs. Finally, an increasingly popular method (RADseq) is used to develop SNP markers, but it was shown that using RADseq data to estimate diversity directly biases estimates [15]. Workflows to implement statistical methods that correct for diversity biases estimates now need an implementation for biologists.

SERPICO Project-Team

4. Application Domains

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

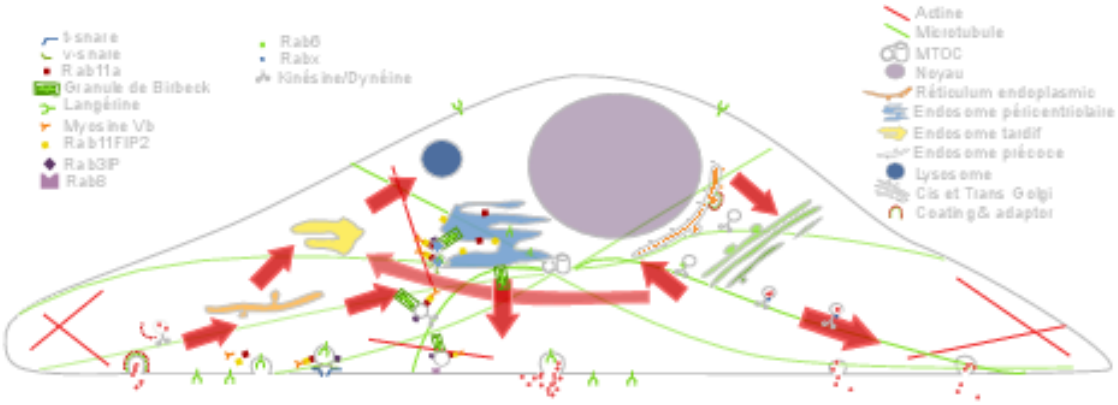

Figure 1. Cargo Langerin Trafficking controlled by Rab11A/Rab11FIP2/MyoVb platform.

In the past recent years, research carried at UMR 144 CNRS-Institut Curie ("Space Time imaging of Endomembranes and organelles Dynamics" team) contributed to a better understanding of the intracellular compartimentation of specialized model cells such as melanocytes and Langerhans cells, the components and structural events involved in the biogenesis of their specialized organelles: melanosomes and Birbeck granules, respectively. These studies have started to highlight: i/ multiple sorting and structural events involved in the biogenesis of these organelles; ii/ complexity of the endo-melanosomal network of these highly specialized cells; iii/ complex molecular architecture organizing and coordinating their dynamics; iv/ intracellular transport steps affected in genetic diseases, among which the Hermansky Pudlak syndrome (HPS) or involved in viral infection (HIV and Langerin in Langerhans cells).

In this context, the central aim of SERPICO is to understand how the different machineries of molecular components involved are interconnected and coordinated to generate such specialized structures. We need to address the following topics:

1. developing new bioimaging approaches to observe and statistically analyze such coordinated dynamics in live material;
2. correlating this statistically relevant spatiotemporal organization of protein networks with the biological architectures and at the ultrastructural level;
3. modeling intracellular transport of those reference biological complex systems and proposing new experimental plans in an iterative and virtuous circle;
4. managing and analyzing the workflow of image data obtained along different multidimensional microscopy modalities.

These studies are essential to unravel the complexity of the endomembrane system and how different machineries evolve together (e.g. see Fig. 1). They help to control cell organization and function at different scales through an integrative workflow of methodological and technological developments.

At long term, these studies will shed light on the cellular and molecular mechanisms underlying antigen presentation, viral infection or defense mechanisms, skin pigmentation, the pathogenesis of hereditary genetic disorders (lysosomal diseases, immune disorders) and on the mechanisms underlying cell transformation. Our methodological goal is also to link dynamics information obtained through diffraction limited light microscopy, eventually at a time regime compatible with live cell imaging. The overview of ultrastructural organization will be achieved by complementary electron microscopical methods. Image visualization and quantitative analysis are of course important and essential issues in this context.

4.2. Imaging and analysis of cytokskeleton dynamics during cell migration

The ability to migrate in space is among the most fundamental functions of eukaryotic cells and thus is one of the best-studied phenomena in biology. During embryonic development, cell movements result in a massive reorganization of the embryo, from a simple spherical ball of cells into a multi-layered organism; many of the cells at or near the surface of the embryo move to a new, more interior location. Moreover, inadequate or inappropriate migration of immune cells is also critically important for the delivery of protective immune responses to tissues and for wound healing. Finally, cell migration may facilitate the dissemination of tumor cells in blood and organs and eventually the formation of secondary tumors and metastases.

It has been established that the cytoskeleton, composed of actin filaments, microtubules and intermediate filaments (elongated structures with a diameter of a few dozens of nanometers), is essential for several cell mechanisms, including cell migration, cell division and molecule trafficking:

- i/ the actin filaments promote cell protrusion, adhesion and retraction;
- ii/ the microtubules are the support of molecule traffic and cell polarization;
- iii/ the intermediate filaments are hypothesized to control microtubule organization.

Nevertheless, the mechanical and chemical states of migrating cells under various external conditions remain largely unknown. In the last decade, high-resolution microscopy methods led to the discovery of novel aspects of cell migration. Most approaches and models are limited to migration in 2D, justified by the flatness of the cell-motile mechanisms. However, the mechanical patterns that govern migration in 2D models are often not essential for efficient migration in 3D. Accordingly, recent very challenging 3D models of cells moving on flat surfaces have begun to emerge. The key challenge, however, is to understand how a 3D motile cell crawls through the 3D extracellular matrix.

The objective of SERPICO is to develop high-end signal processing and computer vision tools to unfold the dynamical coordination of microtubules, actin filaments and intermediate filaments in 3D, involved in cell migration, cell division and molecule trafficking.

TAPDANCE Team (section vide)

VIRTUAL PLANTS Project-Team (section vide)

ARAMIS Project-Team

4. Application Domains

4.1. Introduction

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

- better understanding the pathophysiology of brain disorders;
- designing biomarkers of pathologies for diagnosis, prognosis and assessment of drug efficacy;
- developping brain computer interfaces for clinical applications;
- improving the localisation of stimulation targets in Deep Brain Stimulation protocol.

These applications are developed in close collaboration with biomedical researchers of the ICM and clinicians of the Pitié-Salpêtrière hospital.

4.2. Understanding brain disorders

The approaches that we develop allow to characterize anatomical and functional alterations, thus making it possible to study these alterations in different clinical populations. This can provide provide new insights into the mechanisms and progression of brain diseases. This typically involves the acquisition of neuroimaging data in a group of patients with a given pathology and in a group of healthy controls. Measures of anatomical and functional alterations are then extracted in each subject (for instance using segmentation of anatomical structures, shape models or graph-theoretic measures of functional connectivity). Statistical analyses are then performed to identify: i) significant differences between groups, ii) correlations between anatomical/functional alterations on the one hand, and clinical, cognitive or biological measures on the other hand, iii) progression of alterations over time.

We propose to apply our methodologies to study the pathophysiology of neurodegenerative diseases (mostly Alzheimer's disease and fronto-temporal dementia), epilepsy, cerebrovascular pathologies and neurodevelopmental disorders (Gilles de la Tourette syndrome). In neurodegenerative diseases, we aim at establishing the progression of alterations, starting from the early and even asymptomatic phases. In Gilles de la Tourette syndrome, we study the atypical anatomical patterns that may contribute to the emergence of symptoms. In epilepsy, we aim at studying the relationships between the different functional and structural components of epileptogenic networks.

4.3. Biomarkers for diagnosis, prognosis and clinical trials

Currently, the routine diagnosis of neurological disorders is mainly based on clinical examinations. This is also true for clinical trials, aiming to assess the efficacy of new treatments. However, clinical diagnoses only partially overlap with pathological processes. For instance, the sensitivity and specificity of clinical diagnosis of Alzheimer's disease (AD) based on established consensus criteria are of only about 70-80% compared to histopathological confirmation. Furthermore, the pathological processes often begin years before the clinical symptoms. Finally, clinical measures embed subjective aspects and have a limited reproducibility and are thus not ideal to track disease progression. It is thus crucial to supplement clinical examinations with biomarkers that can detect and track the progression of pathological processes in the living patient. This has potentially very important implications for the development of new treatments as it would help: i) identifying patients with a given pathology at the earliest stage of the disease, for inclusion in clinical trials; ii) providing measures to monitor the efficacy of treatments.

The derivation of biomarkers from image analysis approaches requires large-scale validation in well-characterized clinical populations. The ARAMIS team is strongly engaged in such efforts, in particular in the field of neurodegenerative disorders. To that purpose, we collaborate to several national studies (see section Partnerships) that involve multicenter and longitudinal acquisitions. Moreover, ARAMIS is strongly involved in the CATI which manages over 15 multicenter studies, including the national cohort MEMENTO (2000 patients).

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 base 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. The BCI approaches that we develop are based on the characterization of the information contained in the functional connectivity patterns. We expect to significantly increase the performance of the BCI system with respect to the sole use of standard power spectra of the activity generated by single local brain areas. Such an improvement will concretely provide the user with a more precise control of the external environment in open-loop BCI tasks and a more coherent feedback in the closed-loop BCI schemes.

4.5. Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a surgical technique, which consists in sending electrical impulses, through implanted electrodes, to specific parts of the brain for the treatment of movement and affective disorders. The technique has been initially developped for otherwise-treatment-resistant patients with essential tremors or Parkinson's disease. Its benefit in other affections, such as dystonia, obsessive-compulsive disorders, Tourette syndrome is currently investigated. The localisation of the stimulation target in specific nucleus in deep brain regions is key to the success of the surgery. This task is difficult since the target nucleus, or the precise sub-territory of a given nucleus is rarely visible in the Magnetic Resonance Image (MRI) of the patients. To address this issue, a possible technique is to personalize a high-resolution histological atlas of the brain to each patient. This personalization is achieved by registering the histological atlas, which consists of an image and meshes of deep brain structures, to the pre-operative MRI of each patient. The registration is currently done by optimally aligning image intensities in the atlas and patient's MRI using a block-matching algorithm. The linear nature of the transform makes the technique robust at the cost of a lack of precision, especially for elderly patients with expanded ventricles. We investigate the use of non-linear registration techniques to optimally align both image intensities and contours of visible structures surrounding the target. We expect to improve the localisation of the target for patients with large ventricles while keeping the method robust in all cases.

ASCLEPIOS Project-Team (section vide)

ATHENA Project-Team

4. Application Domains

4.1. Applications of diffusion MRI

Clinical domain: Diagnosis of neurological disorder
Various examples of CNS diseases as Alzheimer's and Parkinson's diseases and others like multiple sclerosis, traumatic brain injury and schizophrenia have characteristic abnormalities in the micro-structure of brain tissues that are not apparent and cannot be revealed reliably by standard imaging techniques. Diffusion MRI can make visible these co-lateral damages to the fibers of the CNS white matter that connect different brain regions. This is why in our research, Diffusion MRI is the major anatomical imaging modality that will be considered to recover the CNS connectivity.

4.2. Applications of M/EEG

Applications of EEG and MEG:
Clinical domain: Diagnosis of neurological disorders
The dream of all M/EEG researchers is to alleviate the need for invasive recordings (electrocorticograms or intracerebral electrodes), which are often necessary prior to brain surgery, in order to precisely locate both pathological and vital functional areas. We are involved in this quest, particularly through our collaborations with the La Timone hospital in Marseille.
Subtopics include:

- Diagnosis of neurological disorders such as epilepsy, schizophrenia, tinnitus, ...
- Presurgical planning of brain surgery.

Cognitive research

- Aims at better understanding the brain spatio-temporal organisation.
- Collaboration with the *Laboratory for Neurobiology of Cognition* in order to develop methods that suit their needs for sophisticated data analysis.

Brain Computer Interfaces (BCI) aim to allow direct control of external devices using brain signals such as measured through EEG. In our project, BCI can be seen as an application of EEG processing techniques, but also as an object of fundamental and applied research as they open the way for more dynamical and active brain cognitive protocols.

We are developing research collaborations with the Neurelec company in Sophia Antipolis (subsidiary of Oticon Medical) and with the leading EEG software company BESA based in Munich. We collaborate with Nice University Hospital on the usage of BCI-based communication for ALS [0] patients.

[0] Nice University Hospital hosts a regional reference center for patients suffering from Amyotrophic Lateral Sclerosis

BIOVISION Team

4. Application Domains

4.1. High tech vision aid systems for low vision patients

Vision aid systems for low vision patients is an application domain with commercial products already existing. A variety of solutions are on the market and can be distinguished by their functioning (in virtual or augmented reality), the tasks targeted by the systems (e.g., face and object recognition, reading), the platform they use (dedicated platform or general existing one). Our goal is to propose competing solutions based on wide-spread and cheap platforms (e.g., mobile phone and cheap headset) to facilitate transfer to consumer market.

4.2. Human vision understanding through joint experimental and modeling studies, for normal and distrophic retinas

4.2.1. Cells characterization from their spike response

A prior step toward understanding how the retina extracts the information from a visual scene is the characterization of retinal ganglion cells receptive fields. The receptive field allows to classify retinal ganglion cells in sub-types such as direction sensitive cells. Each of these type extracts a local and definite piece of information from the visual scene, transmitted to the visual cortex. Hence receptive fields are somewhat the fundamental bricks of vision.

Current techniques of receptive fields estimation are based on Spike-Triggered Average [70]. However, this method heavily relies on the assumption that the static non linearity is convex (typically this is an exponential). Unfortunately, this violates a fundamental biophysical property of neurons: firing rate is bounded due to the refractory period. Additionally, this method is slow and of low precision.

We are working on more efficient techniques based on non-convex analysis, faster, more precise, and working for a non-convex (typically sigmoidal) non linearity. Additionnally we are also working on designing better stimuli for receptive fields estimations.

4.2.2. Understanding the role of spatio-temporal correlations in visual scene encoding

Retinal response to stimuli is related, on one hand, to spatio-temporal correlations of the stimulus [76], and, on the other hand to the intrinsic spatio-temporal correlations of the retinal activity induced by its vertical and lateral connectivity [81]. However, the role of spatio-temporal correlations in retinal coding is still controversial. With the current evolution of multi-electrode arrays recordings, it is possible to record from tens to thousands of neurons [42], [51], [63], [86], studying not only the correlations between few neurons, but also the correlations present in a whole population of retinal ganglion cells [73], [75], [77], [80]. The BIOVISION team has proposed a framework to study this correlation structure using Gibbs distributions (Sec. 3.2.4). Based upon the mathematical results presented in the papers [5] [45], we have developed algorithms to analyse and reproduce spatio-temporal correlations in neural assemblies containing up to a few hundreds of neurons [13], [69], [68].

We are now applying these methods for the analysis of retina data so as to better understand the role of spatio-temporal spike correlations in vision encoding.

4.2.3. Retinal waves

Retinal waves are bursts of activity occurring spontaneously in the developing retina of vertebrate species, contributing to the shaping of the visual system organization: retina circuitry shaping, retinotopy, eye segregation [83], [52], [74], [53]. They stop a few weeks after birth. Wave activity begins in the early development, long before the retina is responsive to light. It was recently found that they can be reinitiated pharmacologically in the adult mammalian retina [48]. This could have deep consequences on therapy for several degenerative retinal diseases. The mechanism of their generation, in imature, or adult retinas, remains however incompletely understood [84].

We aim at proposing a dynamical model of retinal waves depending on a few canonical parameters (e.g. concentration of a pharmacological agent) controlling the arousal of retinal waves as well as their shape/intensity. We want, on one hand, to design a model sufficiently close to biophysics so that it can reproduce and predict experimental results, and, on the other hand, sufficiently general to provide a generic mechanisms of retinal waves arousal also describing their different types.

4.2.4. Trajectory anticipation, from retina to V1

Global motion processing is a major computational task of biological visual systems. When an object moves across the visual field, the sequence of visited positions is strongly correlated in space and time, forming a trajectory. These correlated images generate a sequence of local activation of the feedforward stream. At the present stage of knowledge, it is still unclear how the early visual system processes motion trajectories. Motion integration, anticipation and prediction would be jointly achieved through the interactions between feed-forward, lateral and feedback propagations within a common spatial reference frame, the retinotopic maps. Addressing this problem is particularly challenging, as it requires to probe these sequences of events at multiple scales (from individual cells to large networks) and multiple stages (retina, primary visual cortex (V1)).

In the context of the ANR Trajectory we are working on such an integrated approach. We aim at modelling the population responses at two key stages of visual motion encoding: the retina and V1 based on simultaneous micro- and mesoscopic recordings made by our partners Institut des Neurosciences de la Timone and Institut de la Vision, and design a simulator of retinal output feeding V1. This study is a step toward understanding mechanisms of motion coding and anticipation with strong impact on our understanding of the visual system.

4.2.5. Simulating and analysing retina's response to visual stimuli

We want to design a retina simulator integrating the most recent advances on retina modeling. We will propose a user-friendly simulator, using parallel (multi-threads) programming, in order to simulate rapidly a large piece of the retina. This platform is further described in the section Software.

CAMIN Team

4. Application Domains

4.1. Non invasive stimulation (external FES)

Both triggered open-loop and closed-loop FES controllers that we are developing for movement involve several sensors and stimulators whose activities must be precisely coordinated by the controller. For instance, the stimulation controller is fed back by various sensors, such as limb joint angles, IMUs providing accelerations, and electrophysiological signals like EMG. These signals are then used by feedback controllers to accurately control the artificially actuated limbs by means of stimulators. This distributed architecture is often deployed on a wireless network since it distinctively complies with mobility constraints, leading to good acceptance from human users. The quality of service (QoS) of this network influences the controlled system properties and the quality of control (QoC). The control performance and robustness of this system can be very far from expectations if implementation-induced disturbances are not taken into account. Thus, the overall performance of a real-time control system must be assessed not only with respect to deadlines (as in classical scheduling analysis) but also by considering other criteria such as time-varying delays and jitter. Hence, research on the joint design of control, computation and communication has to be carried out and applied [49] to the particular case of FES control loops distributed over imperfect links and low power nodes. In addition to the elaboration or adaptation of algorithms, specific tools must be further developed to assess the effectiveness of the new control algorithms and to support their implementation. In particular, realistic simulations remain a precious tool ahead of real experiments to ensure that the implementation meets the functional and safety requirements without danger. This is, for example, the case of the hybrid simulation framework of our distributed FES system currently under development [6]. Understanding and modeling the influence of an implementation (support system) on QoC is a challenging objective in a distributed control design process, but it is mandatory to guarantee the system's safety and effectiveness.

4.2. Invasive stimulation (implanted FES)

Invasive FES means that the selectivity issue has to be dealt with, both from theoretical and technological points of view. To take advantage of spatial and topological nerve organization, invasive stimulation must be able to focus the current in specific nerve areas to elicit subgroups of muscles, while avoiding undesired functional effects (i.e., undesired fiber recruitment). Although multipolar electrodes are available, it is still challenging to find the optimal electrode configuration to reach the given 3D current spreading (i.e., selective stimulus). Indeed, this is not intuitive and modeling is mandatory. On the other hand, implantable stimulators must provide for both dynamical electrode configuration and a complex stimulation profile.

Selectively activating part of the nerve requires an active contact configuration (anode, cathode, high impedance), distribution of the current over the selected contacts, and accurate control of the overall total injected current, both from amplitude and time dimensions. To meet these needs, the neurostimulator has been designed based on a 2-stage device [50]. The first stage is the output stage based on a dedicated analog ASIC (application-specific integrated circuit) that is able to drive 12 channels of stimulation in absolute synchronization, with a programmable and controlled current distribution over selected contacts. The latest ASIC version we designed is CORAIL (circuit fabrication by November 2016): this analog/digital integrated circuit ensures current distribution but also such features as the storage of multiple electrode configurations and the possibility to internally combine poles. The second stage consists of a digital architecture embedded in an FPGA containing a dedicated processor for programming complex stimulation profiles, a monitoring module ensuring the respect of safety constraints stemming from both target tissue protection and electrode integrity preservation (in terms of quantity of injected charge limits), and a protocol stack for remote programming and online control of stimulation parameters. This complex digital system was formally developed using HILECOP §6.1.1 .

GALEN Project-Team

4. Application Domains

4.1. Testing for Difference in Functional Brain Connectivity

Paticipants: Eugene Belilovsky, Matthew Blaschko Collaboration with Inria Parietal: Gael Varoquaux

Proposed a new algorithm for determining the differences in functional brain connectivity between two populations. The aim of our work was to leverage assumptions and show a method that can efficiently provide significance results in the form of (p-values). We demonstrated that our approach works well in practice and simulation and can provide faithful p-values on complicated fMRI data.

4.2. Lung Tumor Detection and Characterization

Paticipants: Evgenios Kornaropoulos, Evangelia Zacharaki, Nikos Paragios

The use of Diffusion Weighted MR Imaging (DWI) is investigated as an alternative tool to radiologists for tumor detection, tumor characterization, distinguishing tumor tissue from non-tumor tissue, and monitoring and predicting treatment response. In collaboration with Hôpitaux Universitaires Henri-Mondor in Paris, France and Chang Gung Memorial Hospital – Linkou in Taipei, Taiwan we investigate the use of model-based methods of 3D image registration, clustering and segmentation towards the development of a framework for automatic interpretation of images, and in particular extraction of meaningful biomarkers in aggressive lymphomas [23][24]. In [23] we combine deformable group-wise registration with a physiological model in order to better estimate diffusion in Diffusion-Weighted MRI, whereas in [24] we explicitly model the diffusion coefficients by a high-order MRF-based joint deformable registration and labeling scheme.

4.3. Protein function prediction

Paticipants: Evangelia Zacharaki, Nikos Paragios (in collaboration with D. Vlachakis, University of Patras, Greece)

The massive expansion of the worldwide Protein Data Bank (PDB) provides new opportunities for computational approaches which can learn from available data and extrapolate the knowledge into new coming instances. The aim of our work in [14] was to exploit experimentally acquired structural information of enzymes through machine learning techniques in order to produce models that predict enzymatic function.

4.4. Imaging biomarkers for chronic lung diseases

Paticipants: Guillaume Chassagnon, Evangelia Zacharaki, Nikos Paragios

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

4.5. Co-segmentation and Co-registration of Subcortical Brain Structures

Paticipants: Enzo Ferrante, Nikos Paragios, Iasonas Kokkinos

New algorithms to perform co-segmentation and co-registration of subcortical brain structures on MRI images were investigated in collaboration with Ecole Polytechnique de Montreal and the Sainte-Justine Hospital Research Center from Montreal [40]. Brain subcortical structures are involved in different neurodegenerative and neuropsychiatric disorders, including schizophrenia, Alzheimers disease, attention deficit, and subtypes of epilepsy. Segmenting these parts of the brain enables a physician to extract indicators, facilitating their quantitative analysis and characterization. We are investigating how estimated maps of semantic labels (obtained using machine learning techniques) can be used as a surrogate for unlabelled data. We are exploring how to combine them with multi-population deformable registration to improve both alignment and segmentation of these challenging brain structures.

MATHNEURO Team (section vide)

MIMESIS Team (section vide)

MNEMOSYNE Project-Team

4. Application Domains

4.1. Overview

One of the most original specificity of our team is that it is part of a laboratory in Neuroscience (with a large spectrum of activity from the molecule to the behavior), focused on neurodegenerative diseases and consequently working in tight collaboration with the medical domain. As a consequence, neuroscientists and the medical world are considered as the primary end-users of our researches. Beyond data and signal analysis where our expertise in machine learning may be possibly useful, our interactions are mainly centered on the exploitation of our models. They will be classically regarded as a way to validate biological assumptions and to generate new hypotheses to be investigated in the living. Our macroscopic models and their implementation in autonomous robots will allow an analysis at the behavioral level and will propose a systemic framework, the interpretation of which will meet aetiological analysis in the medical domain and interpretation of intelligent behavior in cognitive neuroscience.

The study of neurodegenerative diseases is targeted because they match the phenomena we model. Particularly, the Parkinson disease results from the death of dopaminergic cells in the basal ganglia, one of the main systems that we are modeling. The Alzheimer disease also results from the loss of neurons, in several cortical and extracortical regions. The variety of these regions, together with large mnesic and cognitive deficits, require a systemic view of the cerebral architecture and associated functions, very consistent with our approach.

Of course, numerical sciences are also impacted by our researches, at several levels. At a global level, we will propose new control architectures aimed at providing a higher degree of autonomy to robots, as well as machine learning algorithms working in more realistic environment. More specifically, our focus on some cognitive functions in closed loop with a real environment will address currently open problems. This is obviously the case for planning and decision making; this is particularly the case for the domain of affective computing, since motivational characteristics arising from the design of an artificial physiology allow to consider not only cold rational cognition but also hot emotional cognition. The association of both kinds of cognition is undoublty an innovative way to create more realistic intelligent systems but also to elaborate more natural interfaces between these systems and human users.

At last, we think that our activities in well-founded distributed computations and high performance computing are not just intended to help us design large scale systems. We also think that we are working here at the core of informatics and, accordingly, that we could transfer some fundamental results in this domain.

NEUROSYS Project-Team

4. Application Domains

4.1. General remarks

The research directions of the team are motivated by general anaesthesia (GA) that has attracted our attention in the last years. The following paragraphs explain in some detail the motivation of our work on the four major phenomena of GA: loss of consciousness, immobility, amnesia and analgesia.
During general anaesthesia, the electroencephalogram (EEG) on the scalp changes characteristically: increasing the anaesthetic drug concentration the amplitudes of oscillations in the α-band ($\sim 8-12$Hz) and in the $\delta-$band ($2-8$Hz) increase amplitudes in frontal electrodes at low drug concentrations whereas the spectral power decreases in the $\gamma-$band ($\sim 20-60$Hz). This characteristic change in the power is the basis of today's EEG-monitors that assist the anaesthetist in the control of the anaesthesia depths of patients during surgery. However, the conventional monitors exhibit a large variability between the detected anaesthetic depth and the real depth of patients. Moreover, a certain number of patients re-gain consciousness during surgery (about $1-2$ out of 1000) and a large percentage of patients suffer from diverse after-effects, such as nausea or long-lasting cognitive impairments such as partial amnesia (from days to weeks). Since surgery under general anaesthesia is part of a hospital's everyday practice, a large number of patients suffer from these events every day. One reason for the lacking control of such disadvantageous effects is the dramatic lack of knowledge on what is going on in the brain during general anaesthesia and a weak EEG-online monitoring system during anaesthesia. Consequently, to improve the situation of patients during and after surgery and to develop improved anaesthetic procedures or even drugs, research is necessary to learn more about the neural processes in the brain and develop new monitoring machines.

4.2. Level of consciousness

The EEG originates from coherent neural activity of populations in the cortex. Hence to understand better the characteristic power changes in EEG during anaesthesia, it is necessary to study neural population dynamics subject to the concentration of anaesthetic drugs and their action on receptors on the single neuron level. We study mathematical models which will be constrained by the signal features extracted from experimental data, such as EEG (data provided by Jamie Sleigh, University of Auckland and Christoph Destrieux, University of Tours), Local Field Potentials (data provided by Flavio Fröhlich, University of North Carolina - Chapel Hill) and behavior. The combination of model and analysis of experimental data provides the optimal framework to reveal new knowledge on the neural origin of behavioral features, such as the loss of consciousness or the uncontrolled gain of consciousness during surgery. For instance, modelling studies show that the characteristic changes of spectral power (second-order statistics) are not sufficient to deduce all underlying neural mechanisms. Consequently, additional higher-order statistical measures may provide additional insight into underlying neural mechanisms and may provide a novel marker for the loss of consciousness.

Moreover, the constant supervision of anesthetized patients in intensive care is a demanding task for the personnel in hospital practice. It is almost not possible to take care of a patient constantly and hence the todays' medicine demands monitoring devices that control automatically the level of anaesthetic drugs based on the patients' neural activity (e.g., EEG). Brain-Computer-Interfaces (BCI) have already demonstrated their potential for the detection of consciousness in non-responsive patients. We will apply the data analysis techniques known in BCI to extract new markers for the depth of anaesthesia. More specifically, for deeper anaesthesia, auditory-evoked and Event-Related Desynchronization/Event-Related Synchronization (ERD/ERS) BCI could be used to better identify the state of consciousness in patients under anaesthesia. In this context, we have established a first contact to the University of Würzburg. Another research direction will link intracranial EEG and scalp EEG by characterising micro-awake episodes during sleep.

4.3. Immobility

A research direction will be to take benefit of the relationship between the motor activity and anesthesia. Indeed, even if no movement is visually perceptible, a study by electroencephalographic recordings of brain activity in motor areas, quantifying the characteristics of amplitude and phase synchronization observed in the alpha and beta frequency bands, may reveal an intention of movement. This feature is important because it demonstrates that the patient is aware. Thus, we will develop an experimental protocol in collaboration with an anesthesiologist of the regional hospital on stimulating the median nerve at forearm level to track the evolution of the shape of the beta rebound in the motor cortex for various doses of the anesthetic agent.

4.4. Amnesia

Patients sometimes develop post-traumatic disorders associated with the surgery they underwent because they either woke up during the surgery or because the amnesiant effect of the general anaesthesia was only partial, declarative memory being maintained in some unexplained cases. It is still unknown how memory can be maintained under general anaesthesia and it needs to be investigated to improve the recovery from anaesthesia and to avoid as much as possible post-traumatic disorders. To learn more about memory under anaesthesia, we will focus our theoretical studies on the oscillation regimes observed in the hippocampus, mainly in the theta and gamma ranges, which are correlated with memory formation and retrieval.

4.5. Analgesia

One of the most important aspect in general anaesthesia is the loss of pain. During surgery, it is very difficult to find out whether the anesthetized patient feels pain and hence will develop cognitive impairment after surgery. Today, the anesthesiologist knows and detects physiological signs of pain, such as sweat, colour of skin or spontaneous involuntary movements. However, more objective criteria based on EEG may assist the pain detection and hence improves the patients' situation. To this end, we analyze large sets of patient EEG-data observed during surgery and aim to extract EEG signal features of pain.

PARIETAL Project-Team

4. Application Domains

4.1. Cognitive neuroscience

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

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

4.1.2. Analysis of brain Connectivity

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

4.1.3. Modeling of brain processes (MEG)

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

SISTM Project-Team

4. Application Domains

4.1. Systems Biology and Translational medicine

Biological and clinical researches have dramatically changed because of the technological advances, leading to the possibility of measuring much more biological quantities than previously. Clinical research studies can include now traditional measurements such as clinical status, but also thousands of cell populations, peptides, gene expressions for a given patient. This has facilitated the transfer of knowledge from basic to clinical science (from "bench side to bedside") and vice versa, a process often called "Translational medicine". However, the analysis of these large amounts of data needs specific methods, especially when one wants to have a global understanding of the information inherent to complex systems through an "integrative analysis". These systems like the immune system are complex because of many interactions within and between many levels (inside cells, between cells, in different tissues, in various species). This has led to a new field called "Systems biology" rapidly adapted to specific topics such as "Systems Immunology" [47], "Systems vaccinology" [43], "Systems medicine" [32]. From the statistician point of view, two main challenges appear: i) to deal with the massive amount of data ii) to find relevant models capturing observed behaviors.

4.2. The case of HIV immunology

The management of HIV infected patients and the control of the epidemics have been revolutionized by the availability of highly active antiretroviral therapies. Patients treated by these combinations of antiretrovirals have most often undetectable viral loads with an immune reconstitution leading to a survival which is nearly the same to uninfected individuals [39]. Hence, it has been demonstrated that early start of antiretroviral treatments may be good for individual patients as well as for the control of the HIV epidemics (by reducing the transmission from infected people) [31]. However, the implementation of such strategy is difficult especially in developing countries. Some HIV infected individuals do not tolerate antiretroviral regimen or did not reconstitute their immune system. Therefore, vaccine and other immune interventions are required. Many vaccine candidates as well as other immune interventions (IL7, IL15) are currently evaluated. The challenges here are multiple because the effects of these interventions on the immune system are not fully understood, there are no good surrogate markers although the number of measured markers has exponentially increased. Hence, HIV clinical epidemiology has also entered in the era of Big Data because of the very deep evaluation at individual level leading to a huge amount of complex data, repeated over time, even in clinical trials that includes a small number of subjects.

4.3. The case of Ebola vaccine development

In response to the recent outbreak of Ebola virus disease in West Africa, the clinical development of some candidate to Ebola vaccine has been accelerated. Several vectors, mostly encoding glycoprotein of the virus, were tested in Phase I-II studies in order to assess their safety and immunogenicity. One of the main question of interest there is the antibody response induced by vaccination, as some non-human primates studies have shown protection against the virus when antibody levels were high enough. Although bridging studies still have to be developed, antibodies are thus considered as a criterium of interest. The challenge is then to evaluate the durability of the antibody response, whether it be at an individual or population level, in order to evaluate the impact of a vaccine strategy in case of an epidemic. Moreover, we are interested in the factors associated to this antibody response, and even more the other immune markers (from both innate and adaptative immune response) able to predict antibody levels. As those relationship are non-linear, sophisticated statistical and mathematical methods are developed in order to address these questions. A systems medicine approach using multidimensional immunogenicity data from clinical trials and statistical models can help to understand vaccine mechanisms and improve the selection of optimised vaccine strategies for clinical trials.

VISAGES Project-Team

4. Application Domains

4.1. Neuroimaging

One research objective in neuroimaging is the construction of anatomical and functional cerebral maps under normal and pathological conditions. Many researches are currently performed to find correlations between anatomical structures, essentially sulci and gyri, where neuronal activation takes place, and cerebral functions, as assessed by recordings obtained by the means of various neuroimaging modalities, such as PET (Positron Emission Tomography), fMRI (Functional Magnetic Resonance Imaging), EEG (Electro-EncephaloGraphy) and MEG (Magneto-EncephaloGraphy). Then, a central problem inherent to the formation of such maps is to put together recordings obtained from different modalities and from different subjects. This mapping can be greatly facilitated by the use of MR anatomical brain scans with high spatial resolution that allows a proper visualization of fine anatomical structures (sulci and gyri). Recent improvements in image processing techniques, such as segmentation, registration, delineation of the cortical ribbon, modeling of anatomical structures and multi-modality fusion, make possible this ambitious goal in neuroimaging. This problem is very rich in terms of applications since both clinical and neuroscience applications share similar problems. Since this domain is very generic by nature, our major contributions are directed towards clinical needs even though our work can address some specific aspects related to the neuroscience domain.

4.2. Multiple sclerosis

Over the past years, a discrepancy became apparent between clinical Multiple sclerosis (MS) classification describing on the one hand MS according to four different disease courses and, on the other hand, the description of two different disease stages (an early inflammatory and a subsequently neurodegenerative phase). It is to be expected that neuroimaging will play a critical role to define in vivo those four different MS lesion patterns. An in vivo distinction between the four MS lesion patterns, and also between early and late stages of MS will have an important impact in the future for a better understanding of the natural history of MS and even more for the appropriate selection and monitoring of drug treatment in MS patients. MRI has a low specificity for defining in more detail the pathological changes which could discriminate between the different lesion types. However, it has a high sensitivity to detect focal and also widespread, diffuse pathology of the normal appearing white and gray matter. Our major objective within this application domain is then to define new neuroimaging markers for tracking the evolution of the pathology from high dimensional data (e.g. nD+t MRI) in the brain and the spinal cord. In addition, in order to complement MR neuroimaging data, we ambition to perform also cell labeling neuroimaging (e.g. MRI or PET) and to compare MR and PET data using standard and experimental MR contrast agents and radiolabeled PET tracers for activated microglia (e.g. USPIO or PK 11195). The goal is to define and develop, for routine purposes, cell specific and also quantitative imaging markers for the improved in vivo characterization of MS pathology.

4.3. Modeling of anatomical and anatomo-functional neurological patterns

The major objective within this application domain is to build anatomical and functional brain atlases in the context of functional mapping and for the study of developmental, neurodegenerative or even psychiatric brain diseases (Multiple sclerosis, Epilepsy, Parkinson, Dysphasia, Depression or even Alzheimer). This is a very competitive research domain; our contribution is based on our previous works in this field, and by continuing our local and wider collaborations.

An additional objective within this application domain is to find new descriptors to study the brain anatomy and/or function (e.g. variation of brain perfusion, evolution in shape and size of an anatomical structure in relation with pathology or functional patterns, computation of asymmetries ...). This is also a very critical research domain, especially for many developmental or neurodegenerative brain diseases.

XPOP Team

4. Application Domains

4.1. Population pharmacometrics

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

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

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

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

4.2. Precision medicine and pharmacogenomics

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

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

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

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

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

4.3. Biology - Intracellular processes

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

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

AIRSEA Project-Team

4. Application Domains

4.1. The Ocean-Atmosphere System

The evolution of natural systems, in the short, mid, or long term, has extremely important consequences for both the global Earth system and humanity. Forecasting this evolution is thus a major challenge from the scientific, economic, and human viewpoints.

Humanity has to face the problem of **global warming**, brought on by the emission of greenhouse gases from human activities. This warming will probably cause huge changes at global and regional scales, in terms of climate, vegetation and biodiversity, with major consequences for local populations. Research has therefore been conducted over the past 15 to 20 years in an effort to model the Earth's climate and forecast its evolution in the 21st century in response to anthropic action.

With regard to short-term forecasts, the best and oldest example is of course **weather forecasting**. Meteorological services have been providing daily short-term forecasts for several decades which are of crucial importance for numerous human activities.

Numerous other problems can also be mentioned, like **seasonal weather forecasting** (to enable powerful phenomena like an El Niño event or a drought period to be anticipated a few months in advance), **operational oceanography** (short-term forecasts of the evolution of the ocean system to provide services for the fishing industry, ship routing, defense, or the fight against marine pollution) or the prediction of **floods**.

As mentioned previously, mathematical and numerical tools are omnipresent and play a fundamental role in these areas of research. In this context, the vocation of AIRSEA is not to carry out numerical prediction, but to address mathematical issues raised by the development of prediction systems for these application fields, in close collaboration with geophysicists.

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, biogeochemistry of oceans, resilience of society w.r.t. hazardous flows, ...

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 there 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 quasisteady 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 costly and generally not efficient in long term. The objective is to determine a configuration almost stable with 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 origines. 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 the 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.

CASTOR Project-Team (section vide)

CLIME Project-Team

4. Application Domains

4.1. Introduction

The first application domain of the project-team is atmospheric chemistry. We develop and maintain the air quality modeling system Polyphemus, which includes several numerical models (Gaussian models, Lagrangian model, two 3D Eulerian models including Polair3D) and their adjoints, and different high level methods: ensemble forecast, sequential and variational data assimilation algorithms. Advanced data assimilation methods, network design, inverse modeling, ensemble forecast are studied in the context of air chemistry. Note that addressing these high level issues requires controlling the full software chain (models and data assimilation algorithms).

The activity on assimilation of satellite data is mainly carried out for meteorology and oceanography. This is addressed in cooperation with external partners who provide numerical models. Concerning oceanography, the aim is to assess ocean surface circulation, by assimilating fronts and vortices displayed on image acquisitions. Concerning meteorology, the focus is on correcting the location of structures related to high-impact weather events (cyclones, convective storms, etc.) by assimilating images.

4.2. Air quality

Air quality modeling implies studying the interactions between meteorology and atmospheric chemistry in the various phases of matter, which leads to the development of highly complex models. The different usages of these models comprise operational forecasting, case studies, impact studies, etc., with both societal (e.g., public information on pollution forecast) and economical impacts (e.g., impact studies for dangerous industrial sites). Models lack some appropriate data, for instance better emissions, to perform an accurate forecast and data assimilation techniques are recognized as a major key point for improving forecast's quality.

In this context, Clime is interested in various problems, the following being the crucial ones:

- The development of ensemble forecast methods for estimating the quality of the prediction, in relation with the quality of the model and the observations. The ensemble methods allow sensitivity analysis with respect to the model's parameters so as to identify physical and chemical processes, whose modeling must be improved.
- The development of methodologies for sequential aggregation of ensemble simulations. What ensembles should be generated for that purpose, how spatialized forecasts can be generated with aggregation, how can the different approaches be coupled with data assimilation?
- The definition of second-order data assimilation methods for the design of optimal observation networks. The two main objectives are: management of combinations of sensor types, and deployment modes and dynamic management of mobile sensors' trajectories.
- How to estimate the emission rate of an accidental release of a pollutant, using observations and a dispersion model (from the near-field to the continental scale)? How to optimally predict the evolution of a plume? Hence, how to help people in charge of risk evaluation for the population?
- The definition of non-Gaussian approaches for data assimilation.
- The assimilation of satellite measurements of troposphere chemistry.

The activities of Clime in air quality are supported by the development of the Polyphemus air quality modeling system. This system has a modular design, which makes it easier to manage high level applications such as inverse modeling, data assimilation and ensemble forecast.

4.3. Oceanography

The capacity of performing a high quality forecast of the state of the ocean, from the regional to the global scales, is of major interest. Such a forecast can only be obtained by systematically coupling numerical models and observations (in situ and satellite data). In this context, being able to assimilate image structures becomes a key point. Examples of such image structures are:

- apparent motion field that represents surface velocity;
- trajectories, obtained either from tracking of features or from integration of the velocity field;
- spatial objects, such as fronts, eddies or filaments.

Image models of these structures are developed and take into account the underlying physical processes. Image acquisitions are assimilated into these models to derive pseudo-observations of state variables, which are further assimilated in numerical ocean forecast models.

4.4. Meteorology

Meteorological forecasting constitutes a major applicative challenge for image assimilation. Although satellite data are operationally assimilated within models, this is mainly done on an independent pixel basis: the observed radiance is linked to the state variables via a radiative transfer model, that plays the role of an observation operator. Indeed, because of their limited spatial and temporal resolutions, numerical weather forecast models fail to exploit image structures, such as precursors of high impact weather:

- cyclogenesis related to the intrusion of dry stratospheric air in the troposphere (a precursor of cyclones),
- convective systems (supercells) leading to heavy winter time storms,
- low-level temperature inversion leading to fog and ice formation, etc.

To date, there is no available method for assimilating such data, which are characterized by a strong coherence in space and time. Meteorologists have developed qualitative Conceptual Models (CMs), for describing the high impact weathers and their signature on images, and tools to detect CMs on image data. The result of this detection is used for correcting the numerical models, for instance by modifying the initialization. The aim is therefore to develop a methodological framework allowing to assimilate the detected CMs within numerical forecast models. This is a challenging issue given the considerable impact of the related meteorological events.

4.5. 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 develop. Numerical simulation is well established to study the urban environment, e.g., for road traffic modeling. 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. A number of research issues can be raised:

- How to properly take into account the city geometry that makes the data assimilation problems unique?
- How to make use of the various sensors, sometimes mobile, of low quality but numerous?
- How to couple all the systems that are intricated at urban scale?

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

COFFEE Project-Team

4. Application Domains

4.1. Porous Media

Clearly, the analysis and simulation of flows in porous media is a major theme in our team. It is strongly motivated by industrial partnerships, with Total, GdF-Suez, ANDRA, BRGM, etc. with direct applications in geothermy, geological storages, and oil and gas recovery.

Our research has first dealt with the discretization and convergence analysis of multiphase Darcy flows on general polyhedral meshes and for heterogeneous anisotropic media. We have investigated both the Vertex Approximate Gradient (VAG) scheme using both cell and vertex unknowns and the Hybrid Finite Volume (HFV) scheme using both cell and face unknowns. It is remarkable that the VAG scheme is much more accurate than existing nodal approaches (such as CVFE) for heterogeneous test cases: since it avoids the mixing of different rocktypes inside the control volumes, while preserving the low cost of nodal discretizations thanks to the elimination of cell unknowns without any fill-in. The convergence of the numerical discretizations has been studied for the problem of contaminant transport with adsorption in the case of HFV scheme and for two phase Darcy flows in global pressure formulation using particular VAG or HFV schemes, as well as the more general framework of gradient schemes. To reduce the Grid Orientation Effect, a general methodology is proposed in on general meshes. It is based on the recombination of given conservative fluxes to define new conservative fluxes on a richer stencil. On the same token, we have considered the transport of radionucleides by water in porous media. The question is naturally motivated by security studies of nuclear waste storage. We have dealt with the non linear Peaceman system, set on a heterogeneous domain, typically a layered geological medium. The system couples anisotropic diffusion equation and a diffusion-dispersion equation for the pollutant concentration. We have developed and analyzed a specific DDFV scheme to investigate such flows

4.2. Particulate and mixture flows

We investigate fluid mechanics models referred to as “multi–fluids” flows. A large part of our activity is more specifically concerned with the case where a disperse phase interacts with a dense phase. Such flows arise in numerous applications, like for pollutant transport and dispersion, the combustion of fuel particles in air, the modelling of fluidized beds, the dynamic of sprays and in particular biosprays with medical applications, engine fine particles emission... There are many possible modelings of such flows: microscopic models where the two phases occupy distinct domains and where the coupling arises through intricate interface conditions; macroscopic models which are of hydrodynamic (multiphase) type, involving non standard state laws, possibly with non conservative terms, and the so–called mesoscopic models. The latter are based on Eulerian–Lagrangian description where the disperse phase is described by a particle distribution function in phase space. Following this path we are led to a Vlasov-like equation coupled to a system describing the evolution of the dense phase that is either the Euler or the Navier-Stokes equations. It turns out that the leading effect in such models is the drag force. However, the role of other terms, of more or less phenomenological nature, deserves to be discussed (close packing terms, lift term, Basset force...). Of course the fluid/kinetic model is interesting in itself and needs further analysis and dedicated numerical schemes. In particular, in collaboration with the Atomic Energy Commission (CEA), we have proposed a semi-Lagrangian scheme for the simulation of particulate flows, extending the framework established in plasma physics to such flows.

We also think it is worthwhile to identify hydrodynamic regimes: it leads to discuss hierarchies of coupled hydrodynamic systems, the nature of which could be quite intriguing and original, while they share some common features of the porous media problems. We are particularly interested in revisiting the modeling of mixture flows through the viewpoint of kinetic models and hydrodynamic regimes. We propose to revisit the derivation of new mixture models, generalizing Kazhikov-Smagulov equations, through hydrodynamic asymptotics. The model is of "hybrid" type in the sense that the constraint reduces to the standard incompressibility condition when the disperse phase is absent, while it involves derivatives of the particle volume fraction when the disperse phase is present.

4.3. Biological degradation, biofilms formation and algae proliferation

Members of the team have started an original research program devoted to biofilms formation and algae proliferation. We started working on this subject through a collaboration with Roberto Natalini and a group of experts in Firenze interested in preventing damages on historical monuments. It is also motivated by Ostreopsis proliferation in the Mediterranean Sea. The multidisciplinary character of this research relies on discussions with researchers of the Oceanography Laboratory in Villefranche-sur-Mer, a leading marine research unit, and the Inria team BIOCORE, led by J-L Gouzé. This research is supported by a ANR-project, led by M. Ribot, and it is the main topic of the PhD thesis of B. Polizzi.

FLUMINANCE Project-Team

4. Application Domains

4.1. Introduction

By designing new approaches for the analysis of fluid-image sequences the FLUMINANCE group aims at contributing to several application domains of great interest for the community and in which the analysis of complex fluid flows plays a central role. The group focuses mainly on two broad application domains:

- Environmental sciences;
- Experimental fluid mechanics and industrial flows.

We detail hereafter these two application domains.

4.2. Environmental sciences

The first huge application domain concerns all the sciences that aim at observing the biosphere evolution such as meteorology, climatology or oceanography but also remote sensing study for the monitoring of meteorological events or human activities consequences. For all these domains image analysis is a practical and unique tool to *observe, detect, measure, characterize or analyze* the evolution of physical parameters over a large domain. The design of generic image processing techniques for all these domains might offer practical software tools to measure precisely the evolution of fluid flows for weather forecasting or climatology studies. It might also offer possibilities of close surveillance of human and natural activities in sensible areas such as forests, river edges, and valley in order to monitor pollution, floods or fire. The need in terms of local weather forecasting, risk prevention, or local climate change is becoming crucial for our tomorrow's life. At a more local scale, image sensors may also be of major utility to analyze precisely the effect of air curtains for safe packaging in agro-industrial.

4.3. Experimental fluid mechanics and industrial flows

In the domain of **experimental fluid mechanics**, the visualization of fluid flows plays a major role, especially for turbulence study since high frequency imaging has been made currently available. Together with analysis of turbulence at different scales, one of the major goals pursued at the moment by many scientists and engineers consists in studying the ability to manipulate a flow to induce a desired change. This is of huge technological importance to enhance or inhibit mixing in shear flows, improve energetic efficiency or control the physical effects of strain and stresses. This is for instance of particular interest for:

- military applications, for example to limit the infra-red signatures of fighter aircraft;
- aeronautics and transportation, to limit fuel consumption by controlling drag and lift effects of turbulence and boundary layer behavior;
- industrial applications, for example to monitor flowing, melting, mixing or swelling of processed materials, or preserve manufactured products from contamination by airborne pollutants, or in industrial chemistry to increase chemical reactions by acting on turbulence phenomena.

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LEMON Team

4. Application Domains

4.1. Coastal Oceanography

Participants: Fabien Marche, Antoine Rousseau.

Saint-Venant and Boussinesq equations have been widely applied until recently to model and simulate the propagation and transformations of waves in the nearshore area, over rapidly varying topography. However, the first equations do not include dispersive effects, and consequently have a domain of validity limited to the surf zone. The second set of equations overcome the limitations of the SV equations but relies on a "small amplitude assumption" and is therefore unable to model the whole range of waves transformations. This is the reason why they are usually called "weakly nonlinear Boussinesq equations". A better suited set of equations is known as the Green-Naghdi equations, but until recently, they have received far less attention, both from the theoretical and numerical point of view. In particular, there is no available numerical method of arbitrary ordre for 2d simulations on unstructured meshes. Additionally, the construction of rigorous positive preserving schemes is a paramount for the study of waves run-up.

4.2. Urban Floods

Participants: Carole Delenne, Vincent Guinot, Antoine Rousseau.

Floods have been identified by the National Accounting Authority (Cour des Comptes) to represent up to 1% of the GNP in terms of damage cost. For crisis management purposes, modeling urban floods at the scale of the conurbation is highly desirable. This however cannot be achieved in the current state of technology because of the meshing and computational cost (up to one billion cells being needed to mesh an entire urban area). This can be overcome by upscaling the shallow water equations so as to obtain large scale models that can operate three orders of magnitude faster than refined 2D models. Various upscaled versions of the upscaled 2D Shallow Water Equations have been proposed in the literature, some of which by members of the Lemon team. Further developments are being carried out, including the subgrid-scale description of topography variations and a better representation of energy dissipation terms. Laboratory experiments are also needed to discriminate between the various existing models.

4.3. River Hydraulics

Participants: Vincent Guinot, Antoine Rousseau.

Shallow Water (SW) models are widely used for the numerical modeling of river flows. Depending on the geometry of the domain, of the flow regime, and of required accuracy, either 1D or 2D SW models are implemented. It is thus necessary to couple 1D models with 2D models when both models are used to represent different portions of the same river. Moreover, when a river flows into the sea/ocean (e.g. the Rhône river in the Mediterranean), one may need to couple a 2D SW with a full 3D model (such as the Navier-Stokes equations) of the estuary. These issues have been widely addressed by the river-engineering community, but often with somehow crude approaches in terms of coupling algorithms. This may be improved thanks to more advanced boundary conditions, and with the use of Schwarz iterative methods for example.

MAGIQUE-3D Project-Team

4. Application Domains

4.1. Seismic Imaging

The main objective of modern seismic processing is to find the best representation of the subsurface that can fit the data recorded during the seismic acquisition survey. In this context, the seismic wave equation is the most appropriate mathematical model. Numerous research programs and related publications have been devoted to this equation. An acoustic representation is suitable if the waves propagate in a fluid. But the subsurface does not contain fluids only and the acoustic representation is not sufficient in the general case. Indeed the acoustic wave equation does not take some waves into account, for instance shear waves, turning waves or the multiples that are generated after several reflections at the interfaces between the different layers of the geological model. It is then necessary to consider a mathematical model that is more complex and resolution techniques that can model such waves. The elastic or viscoelastic wave equations are then reference models, but they are much more difficult to solve, in particular in the 3D case. Hence, we need to develop new high-performance approximation methods.

Reflection seismics is an indirect measurement technique that consists in recording echoes produced by the propagation of a seismic wave in a geological model. This wave is created artificially during seismic acquisition surveys. These echoes (i.e., reflections) are generated by the heterogeneities of the model. For instance, if the seismic wave propagates from a clay layer to sand, one will observe a sharp reflected signal in the seismic data recorded in the field. One then talks about reflection seismics if the wave is reflected at the interface between the two media, or talks about seismic refraction if the wave is transmitted along the interface. The arrival time of the echo enables one to locate the position of this transition, and the amplitude of the echo gives information on some physical parameters of the two geological media that are in contact. The first petroleum exploration surveys were performed at the beginning of the 1920's and for instance, the Orchard Salt Dome in Texas (USA) was discovered in 1924 by the seismic-reflection method.

4.2. Imaging complex media with ultrasonic waves

The acoustic behavior of heterogeneous or composite materials attracts considerable excitement. Indeed, their acoustic response may be extremely different from the single constituents responses. In particular, dispersions of resonators in a matrix are the object of large research efforts, both experimentally and theoretically. However it is still a challenge to dispose of numerical tools with sufficient abilities to deal with the simulation and imaging of such materials behavior. Indeed, not only acoustic simulations are very time-consuming, but they have to be performed on realistic enough solution domains, i.e. domains which capture well enough the structural features of the considered materials.

This collaboration with I2M, University of Bordeaux aims at addressing this type of challenges by developing numerical and experimental tools in order to understand the propagation of ultrasonic waves in complex media, image these media, and in the future, help design composite materials for industrial purposes.

4.3. Helioseismology

This collaboration with the Max Planck Institute for Solar System, G¨ottingen, Germany, which started in 2014, aims at designing efficient numerical methods for the wave propagation problems that arise in helioseismology in the context of inverse problems. The final goal is to retrieve information about the structure of the Sun i.e. inner properties such as density or pressure via the inversion of a wave propagation problem. Acoustic waves propagate inside the Sun which, in a first approximation and regarding the time scales of physical phenomena, can be considered as a moving fluid medium with constant velocity of motion. Some other simplifications lead to computational saving, such as supposing a radial or axisymmetric geometry

of the Sun. Aeroacoustic equations must be adapted and efficiently solved in this context, this has been done in the finite elements code Montjoie 5.3 . In other situations, a full 3D simulation is required and demands large computational resources. Ultimately, we aim at modeling the coupling with gravity potential and electromagnetic waves (MHD equations) in order to be able to better understand Sun spots.

SERENA Team

4. Application Domains

4.1. Environmental problems

We pursue *applications* of our theoretical results to current challenging *environmental problems* with numerous *academic collaborators* and with *industrial partners* such as ANDRA, IFP Energies Nouvelles, CEA, and EDF. We are traditionally interested in *porous media* for multiphase flows and transport of contaminants in the subsurface and concentrate on fractures, fracture networks, fractured porous media, subsurface depollution after chemical leakage, nuclear waste disposal in deep underground repositories, and geological sequestration of CO_2. Among our newer themes, we count complex inviscid flows interacting with a mechanical deformable structure and Navier–Stokes flows. Such problems are encountered in energy production (operation of nuclear reactors) and safety assessment (shock waves resulting from an explosion impinging on a structure).

STEEP Project-Team

4. Application Domains

4.1. Introduction

In the context described in the previous sections, we can distinguish two connected and complementary strategies for analyzing environmental pressures: a sectorial approach and a spatial one. The first one is more directly connected to ecological accounting, the second one has more direct relations to urban economy and land cover modelling. Let us start by describing the former.

4.2. Ecological accounting for sectorial pressure assessment

One of the major issues in the assessment of the long-term sustainability of urban areas is related to the concept of "imported sustainability". Cities bring in from the outside most of their material and energy resources, and reject to the outside the waste produced by their activity. The modern era has seen a dramatic increase in both volume and variety of these material flows and consumption as well as in distance of origin and destination of these flows, usually accompanied by a spectacular increase in the associated environmental impacts. A realistic assessment of the sustainability of urban areas requires to quantify both local and distant environmental impacts; greenhouse gas emissions are only one aspect of this question. Such an assessment brings to light the most relevant direct and indirect lines of action on these issues. In this respect, it is useful to introduce the alternative concepts of consumer versus producer responsibility (or point of view).

The producer point of view is the most useful to pinpoint relevant direct lines of actions on environmental pressures due to production. In other respects, any territory imports and exports goods and services from and to the rest of the world. The consumer point of view provides information on the indirect pressures associated with these exchanges, as production responds to a final demand. Tracking the various supply chains through the analysis of the structure of the local economy and its relations and dependencies to the external world allows us to identify critically important contributions to environmental pressures; this also enables us to define fair environmental indicators in order not to attribute environmental pressures to producers only (whose responsibility is the easier to quantify of the two). In this approach, the producer responsibility follows directly from the measurement of its energy and material uses, while the consumer responsibility is established indirectly through an allocation of the impacts of production to the final consumers, but this second mode of allocation is to some extent virtual and partly subjective. Four methods stand out:

- Material Flow Analysis (MFA)
- Input-Output Analysis (IOA)
- Life-Cycle Analysis (LCA)
- Ecological Footprint (EF)

Each of these is based on a well-defined structuring element: mass conservation for MFA, measure of industrial inter-dependencies for IOA, identification of all the steps from cradle to grave for LCA, measure of biocapacity demand for EF. The different methods have preferred areas of application. For example, EF is more relevant for analyzing primary production such as agricultural staples, wood, etc. IOA is more focused on whole industrial sectors, while LCA is geared towards end-user products, taken as functional units; finally, primary materials (such as metals), waste and emissions are more easily characterized through MFA. Methodological choices are driven by the type of question one needs to address, data availability and collection method and the spatial scales under consideration. Indeed, data can be used in two different ways: bottom-up or top-down. The bottom-up data is more precise, but in general precludes comprehensiveness; on the contrary, the top-down data is by nature more comprehensive, but is not suited for a detailed, fine-scale analysis of the results.

STEEP is pursuing its research program on this theme with three major goals: 1) Creating a comprehensive database enabling pressure analyses; 2) Developing methodologies and models resolving scaling issues, and developing algorithms allowing us to rigorously and automatically obtain adequate assessments; 3) Providing a synthetic analysis of environmental pressures associated to the major material flows, at various geographic levels (employment catchment area, *département* and *région*, for France), with the explicit aim of incorporating this type of information in the public decision process on environmental issues, via specifically designed decision-help procedures.

4.3. Urban economy and land use/land cover changes: assessment of spatial distributions of the pressures

The preceding section was focused on territorial metabolism, in particular on the analysis of supply chains. Here territories are examined with a more prominent emphasis on their spatial dimension, with attention to: the spatial distribution of local pressures previously identified (from a land use point of view), and the modeling of future land use and activity location (from an economic point of view). These two questions correspond to very different modeling strategies: the first one is more statistical in nature, extrapolating future land use from past evolution combined with global territory scenarios; the other one has a more fundamental flavor and focuses on an understanding of the processes driving urbanization. For this, we focus more precisely on the question of household and businesses choices of localization, as well as on spatial fluxes within the territory (transportation of goods and persons). The critical point here is to understand and manage urban sprawl and its environmental effects (GHG emission, loss of arable land, ecosystem fragmentation, and so on).

4.3.1. Land Use/Land Cover Change models (LUCC)

LUCC models are mostly used in environmental sciences, e.g. to evaluate the impact of climate change on agriculture, but they can also be used to analyze urban sprawl. There is a variety of models, static or dynamic, grid- or agent- based, local or global, etc., and with varying degrees of sophistication concerning spatio-temporal analysis or decision structures incorporated in the model.

The models of interest here are statistical in nature but spatially explicit. Following decades of development, they are robust, versatile and mature. In principle, agent-models have a larger potential for representing decision processes, but in practice this advantage results in a loss of universality of the models. Among the most well-known and most mature models, one can mention the CLUE family of models, DINAMIC, or LCM (Land Change Modeler. These models are well described in the literature, and will only be briefly presented here.

These models analyze change in land use in a statistical way; they are structured around three different modules:

- The first module determines the probability of change of pixels of the territory (pixels are typically tens to hundreds of meters in size).
- The second module defines the global changes between the various land uses of interest per time step (usually, a few years), based on global scenarios of evolution of the territory under study. These first two modules are independent of one another.
- The last module distributes changes of land use in an explicit manner, pixel per pixel, at each time step, on the basis of the information provided by the first two modules.

Probabilities of change are calibrated on past evolution, from the differences between two past maps of land use in the more favorable cases, or from a single map otherwise (under the assumption that the logic of occupation changes is the same as the logic of land use at this single date). Such changes are then characterized in a statistical way with the help of modeling variables identified by the modeler as having potential explaining or structuring power (typically, a few to a dozen variables are used for one type of land use change). For example, in the case of urban sprawl, typical explaining factors are the distance to existing urbanized zones or distances to roads and other means of transportation, elements of real estate costs, etc. Global scenarios are quantified in terms of global changes in land use over the whole studied area (e.g., how many hectares are

transformed from agricultural to urban uses in a given number of years, how does this evolve over time...); this is done either from academic expert knowledge, or from information provided by local planning agencies. Whenever feasible, models are validated by comparing the model predictions with actual evolution at a later date. Therefore, such models need from one to three land use maps at different dates for calibration and validation purposes (the larger the number of maps, the more robust and accurate the model). A large array of statistical tools is available in the literature to perform the calibration and validation of the model.

The horizon of projections of such models is limited in time, typically 20-30 years, due to the inherent uncertainty in such models, although they are occasionally used on longer time-scales. Climate change constraints are included, when needed, through scenarios, as it is not in the scope of such models to incorporate ecological processes that may translate climate change constraints into land cover change dynamics. Note that on such short time-scales, climate change is not dominated by the mean climate evolution but by decade variations which average out on longer time-scales and are not modeled in the global climate models used e.g. for IPCC projections for the end of the century; as a consequence, the various IPCC climate scenarios cannot be distinguished on such a short time horizon.

With regard to LUCC, the STEEP team has been involved for four years in the ESNET project whose funding came to a close in July of 2016, but the scientific production of the project is still underway. This project bears on the characterization of local Ecosystem Services networks; the project has been coordinated by LECA (*Laboratoire d'Ecologie Alpine*), in collaboration with a number of other research laboratories (most notably, IRSTEA Grenoble, besides our team), and in close interaction with a panel of local stakeholders; the scale of interest is typically a landscape (in the ecologic/geographic sense, i.e., a zone a few kilometers to a few tens of kilometers wide). The project aims at developing a generic modelling framework of ecosystem services, and studying their behavior under various scenarios of coupled urban/environment evolution, at the 2030/2040 horizon, under constraints of climate change. The contribution of the STEEP team is centered on the Land Use/Land Cover Change (LUCC) model that will be one of the major building blocks of the whole project modelling effort, with the help of an ESNET funded post-doctoral researcher. In the process, areas of conceptual and methodological improvements of statistical LUCC models have been identified; implementing these improvements will be useful for the LUCC community at large, independently of the ESNET project needs.

4.3.2. Models for Land-Use and Transportation Interactions (LUTI)

Urban transport systems are intricately linked to urban structure and activities, i.e., to land use. Urbanization generally implies an increased travel demand. Cities have traditionally met this additional demand by extending transportation supply, through new highways and transit lines. In turn, an improvement of the accessibility of ever-farther land leads to an expansion of urban development, resulting in a significant feedback loop between transportation infrastructure and land use, one of the main causes of urban sprawl. Transportation models allow us to address questions generally limited to the impacts of new infrastructures, tolls and other legislation on traffic regulation [0], on user behavior [0], or on the environment [0]. LUTI models (Land-Use and Transport Integrated models) can answer a much broader spectrum of issues. For example, they allow us to understand how the localization of households and of economic activities (which generate transportation demand) adapt to changes of transportation supply. They also allow us to assess the impacts of such changes on the increase in real estate value, or more generally on their effects on the economic development of a specific sector or neighborhood. An economic vision interprets all these interactions in terms of equilibrium between demand and supply. Modelling the localization of households and employments (companies) relies on capturing the way stakeholders arbitrate between accessibility, real estate prices, and attractiveness of different areas.

State of the art and operability of LUTI models. The first model that proved able to analyze the interactions between transport and urbanization was developed by Lowry. Since then theories and models have become increasingly complex over time. They can be classified according to different criteria. A first classification

[0] Congestion, cost and time spent for the transport, etc.
[0] Changes in modality choice.
[0] CO2 emissions, air pollution, noise nuisance, etc.

retraces the historic path of these theories and models. They can be associated with one or several of the approaches underlying all present theories: economic base theory and gravity models, Input/Output models and theory of urban rent, and micro-simulations. A second possibility consists in classifying the models according to their aims and means.

Significant scientific progress has been made over the last thirty years. Nevertheless, modelling tools remain largely restricted to the academic world. Today, only seven models have at least had one recent application outside academia or are commercialized or potentially marketable, in spite of the important needs expressed by the urban planning agencies: Cube Land, DELTA, MARS, OPUS/UrbanSim, PECAS, TRANUS and Pirandello.

To guide their choice of a modelling framework, users can rely on various criteria such as the strength of the theoretical framework, the quality and the diversity of the available documentation, the accessibility of the models (is the model freely available? is the code open source? is the software regularly updated and compatible with the recent operating systems?), the functionality and friendliness of user interfaces (existence of graphic user interface, possibility of interfacing with Geographic Information Systems), existence of technical assistance, volume and availability of the data required to implement the model, etc. For example, among the seven models mentioned above, only two are open source and mature enough to meet professional standards: TRANUS and UrbanSim [0]. These two models are very different but particularly representative of the main current philosophies and trends in this scientific domain. Their comparison is informative.

STEEP implication in LUTI modelling. As yet, very few local planning authorities make use of these strategic models, mostly because they are difficult to calibrate and validate. Systematic improvement on these two critical steps would clearly increase the level of confidence in their results; these limitations hinder their dissemination in local agencies. One of the major goals of STEEP is therefore to meet the need for better calibration and validation strategies and algorithms. This research agenda lies at the core of our project CITiES (*ANR Modèles Numériques*). As for LUTI modeling, we have been using the TRANUS model since the creation of our team. We have also been working on UrbanSim from the beginning of the CITiES project. In this framework we work in close collaboration with AURG [0], the local urban planning agency of Grenoble (*Agence d'Urbanisme de la Région Grenobloise*) in order to better understand and to improve the relevance of these tools for such territorial agencies.

[0] http://www.urbansim.org
[0] http://www.aurg.org/

TONUS Team

4. Application Domains

4.1. Controlled fusion and ITER

The search for alternative energy sources is a major issue for the future. Among others, controlled thermonuclear fusion in a hot hydrogen plasma is a promising possibility. The principle is to confine the plasma in a toroidal chamber, called a tokamak, and to attain the necessary temperatures to sustain nuclear fusion reactions. The International Thermonuclear Experimental Reactor (ITER) is a tokamak being constructed in Cadarache, France. This was the result of a joint decision by an international consortium made of the European Union, Canada, USA, Japan, Russia, South Korea, India and China. ITER is a huge project. As of today, the budget is estimated at 20 billion euros. The first plasma shot is planned for 2020 and the first deuterium-tritium operation for 2027.

Many technical and conceptual difficulties have to be overcome before the actual exploitation of fusion energy. Consequently, much research has been carried out around magnetically confined fusion. Among these studies, it is important to carry out computer simulations of the burning plasma. Thus, mathematicians and computer scientists are also needed in the design of ITER. The reliability and the precision of numerical simulations allow a better understanding of the physical phenomena and thus would lead to better designs. TONUS's main involvement is in such research.

The required temperatures to attain fusion are very high, of the order of a hundred million degrees. Thus it is imperative to prevent the plasma from touching the tokamak inner walls. This confinement is obtained thanks to intense magnetic fields. The magnetic field is created by poloidal coils, which generate the toroidal component of the field. The toroidal plasma current also induces a poloidal component of the magnetic field that twists the magnetic field lines. The twisting is very important for the stability of the plasma. The idea goes back to research by Tamm and Sakharov, two Russian physicists, in the 1950's. Other devices are essential for the proper operation of the tokamak: divertor for collecting the escaping particles, microwave heating for reaching higher temperatures, fuel injector for sustaining the fusion reactions, toroidal coils for controlling instabilities, etc.

4.2. Other applications

The software and numerical methods that we develop can also be applied to other fields of physics or of engineering.

- For instance, we have a collaboration with the company AxesSim in Strasbourg for the development of efficient Discontinuous Galerkin (DG) solvers on hybrid computers. The applications is electromagnetic simulations for the conception of antenna, electronic devices or aircraft electromagnetic compatibility.
- The acoustic conception of large rooms requires huge numerical simulations. It is not always possible to solve the full wave equation and many reduced acoustic models have been developed. A popular model consists in considering "acoustic" particles moving at the speed of sound. The resulting Partial Differential Equation (PDE) is very similar to the Vlasov equation. The same modeling is used in radiation theory. We have started to work on the reduction of the acoustic particles model and realized that our reduction approach perfectly applies to this situation. A new PhD with CEREMA (Centre d'études et d'expertise sur les risques, l'environnement, la mobilité et l'aménagement) has started in October 2015 (thesis of Pierre Gerhard). The objective is to investigate the model reduction and to implement the resulting acoustic model in our DG solver.

BIOCORE Project-Team

4. Application Domains

4.1. Bioenergy

Finding sources of renewable energy is a key challenge for our society. We contribute to this topic through two main domains for which a strong and acknowledged expertise has been acquired over the years. First, we consider anaerobic digesters, the field of expertise of the members of the team at the Laboratory of Enviromental Biotechnology (LBE), for the production of methane and/or biohydrogen from organic wastes. The main difficulty is to make these processes more reliable and exploit more efficiently the produced biogas by regulating both its quality and quantity despite high variability in the influent wastes. One of the specific applications that needs to be tackled is the production of biogas in a plant when the incoming organic waste results from the mixing of a finite number of substrates. The development of control laws that optimize the input mix of the substrates as a function of the actual state of the system is a key challenge for the viability of this industry.

The second topic consists in growing microalgae, the field of expertise of the members of the team at the Oceanographic Laboratory of Villefranche-sur-Mer (LOV), to produce biofuel. These microorganisms can synthesize lipids with a much higher productivity than terrestrial oleaginous species. The difficulty is to better understand the involved processes, which are mainly transient, to stimulate and optimize them on the basis of modeling and control strategies. Predicting and optimizing the productivity reached by these promising systems in conditions where light received by each cell is strongly related to hydrodynamics, is a crucial challenge.

Finally, for the energy balance of the process, it is important to couple microalgae and anaerobic digestion to optimize the solar energy that can be recovered from microalgae, as was explored within the ANR Symbiose project (2009-2012) [2].

4.2. CO_2 fixation and fluxes

Phytoplanktonic species, which assimilate CO_2 during photosynthesis, have received a lot of attention in the last years. Microalgal based processes have been developed in order to mitigate industrial CO_2. As for biofuel productions, many problems arise when dealing with microalgae which are more complex than bacteria or yeasts. Several models have been developed within our team to predict the CO_2 uptake in conditions of variable light and nitrogen availability. The first modeling challenge in that context consists in taking temperature effects and light gradient into account.

The second challenge consists in exploiting the microalgal bioreactors which have been developed in the framework of the quantification of carbon fluxes between ocean and atmospheres. The SEMPO platform (simulator of variable environment computer controlled), developed within the LOV team, has been designed to reproduce natural conditions that can take place in the sea and to accurately measure the cells behavior. This platform, for which our team has developed models and control methods over the years, is an original and unique tool to develop relevant models which stay valid in dynamic conditions. It is worth noting that a better knowledge of the photosynthetic mechanisms and improved photosynthesis models will benefit both thematics: CO_2 mitigation and carbon fluxes predictions in the sea.

4.3. Biological control for plants and micro-plants production systems

This research concentrates on the protection of cultures of photosynthetic organisms against their pests or their competitors. The cultures we study are crop and micro-algae productions. In both cases, the devices are more or less open to the outside, depending on the application (greenhouse/field, photobioreactor/raceway), so that they may give access to harmful pathogens and invading species. We opt for protecting the culture through the use of biocontrol in a broad sense.

In crop production, biocontrol is indeed a very promising alternative to reduce pesticide use: it helps protecting the environment, as well as the health of consumers and producers; it limits the development of resistance (compared to chemicals)... The use of biocontrol agents, which are, generically, natural enemies (predators, parasitoids or pathogens) of crop pests [6], is however not widespread yet because it often lacks efficiency in real-life crop production systems (while its efficiency in the laboratory is much higher) and can fail to be economically competitive. Resistant crops are also used instead of pesticides to control pests and pathogens, but the latter eventually more or less rapidly overcome the resistance, so these crops need to be replaced by new resistant crops. As resistant genes are a potentially limited resource, a challenge is to ensure the durability of crop resistance. Our objective is to propose models that would help to explain which factors are locks that prevent the smooth transition from the laboratory to the agricultural crop, as well as develop new methods for the optimal deployment of the pests natural enemies and of crop resistance.

Microalgae production is faced with exactly the same problems since predators of the produced microalgae (e.g. zooplankton) or simply other species of microalgae can invade the photobioreactors and outcompete or eradicate the one that we wish to produce. Methods need therefore to be proposed for fighting the invading species; this could be done by introducing predators of the pest and so keeping it under control, or by controling the conditions of culture in order to reduce the possibility of invasion; the design of such methods could greatly take advantage of our knowledge developed in crop protection since the problems and models are related.

4.4. Biological depollution

These works will be carried out with the LBE , mainly on anaerobic treatment plants. This process, despite its strong advantages (methane production and reduced sludge production) can have several locally stable equilibria. In this sense, proposing reliable strategies to stabilize and optimise this process is a key issue. Because of the recent (re)development of anaerobic digestion, it is crucial to propose validated supervision algorithms for this technology. A problem of growing importance is to take benefit of various waste sources in order to adapt the substrate quality to the bacterial biomass activity and finally optimize the process. This generates new research topics for designing strategies to manage the fluxes of the various substrate sources meeting at the same time the depollution norms and providing a biogas of constant quality. In the past years, we have developed models of increasing complexity. However there is a key step that must be considered in the future: how to integrate the knowledge of the metabolisms in such models which represent the evolution of several hundreds bacterial species? How to improve the models integrating this two dimensional levels of complexity? With this perspective, we wish to better represent the competition between the bacterial species, and drive this competition in order to maintain, in the process, the species with the highest depollution capability. This approach, initiated in [85] must be extended from a theoretical point of view and validated experimentally.

4.5. Experimental Platforms

To test and validate our approach, we use experimental platforms developed by our partner teams; these are highly instrumented for accurately monitoring the state of biological species:

- At LOV: A photobioreactor (SEMPO) for experimental simulation of the Lagrangian dynamical environment of marine microalgae with computer controlled automata for high frequency measurement and on-line control. This photobioreactor is managed by Amélie Talec and Eric Pruvost.
- At LOV: the Full Spectrum platform is dedicated to experimental pilots for microalgae production. This 60 m2 greenhouse contains four instrumented raceways. The light received by the cultivation devices can be modified with spectral filters. The objective of the platform is to grow algae in outdoor conditions, with the natural fluctuations of light and temperature. Finally this pilot allows to test management strategies in conditions closer to industrial production.
- At LBE: Several pilot anaerobic digesters that are highly instrumented and computerized and the algotron, that is the coupling of a digester and a photobioreactor for microalgae production. Eric Latrille is our main contact for this platform at LBE.

- AT ISA: Experimental greenhouses of various sizes (from laboratory to semi-industrial size) and small scale devices for insect behavior testing. A device for microalgae growth in greenhouses has also been set up at ISA. Christine Poncet is our main contact regarding experimental setups at ISA.

Moreover, we may use the data given by several experimental devices at EPI IBIS/ Hans Geiselmann Laboratory (University J. Fourier, Grenoble) for microbial genomics.

CARMEN Project-Team

4. Application Domains

4.1. Scientific context: the LIRYC

The University Hospital of Bordeaux (*CHU de Bordeaux*) is equipped with a specialized cardiology hospital, the *Hôpital Cardiologique du Haut-Lévêque*, where the group of Professor Michel Haïssaguerre has established itself as a global leader in the field of cardiac electrophysiology. Their discoveries in the area of atrial fibrillation and sudden cardiac death syndromes are widely acclaimed, and the group is a national and international referral center for treatment of cardiac arrhythmia. Thus the group also sees large numbers of patients with rare cardiac diseases.

In 2011 the group has won the competition for a 40 million euro *Investissements d'Avenir* grant for the establishment of IHU Liryc, an institute that combines clinical, experimental, and numerical research in the area of cardiac arrhythmia (http://ihu-liryc.fr). The institute works in all areas of modern cardiac electrophysiology: atrial arrhythmias, sudden death due to ventricular fibrillation, heart failure related to ventricular dyssynchrony, and metabolic disorders. It is recognized as one of the most important centers worldwide in this area.

The Carmen team was founded to partner with IHU Liryc. We aim at bringing applied mathematics and scientific computing closer to experimental and clinical cardiac electrophysiology. In collaboration with experimental and clinical researchers at Liry we aim at enhancing fundamental knowledge of the normal and abnormal cardiac electrical activity and of the patterns of the electrocardiogram, and we will develop new simulation tools for training, biological, and clinical applications.

4.2. Basic experimental electrophysiology

Our modeling is carried out in coordination with the experimental teams from IHU Liryc. It will help to write new concepts concerning the multiscale organisation of the cardiac action potentials and will serve our understanding in many electrical pathologies. For example, we will be modeling the structural heterogeneities at the cellular scale, and at an intermediate scale between the cellular and tissue scales.

At the atrial level, we apply our models to understand the mechanisms of complex arrythmias and the relation with the heterogeneities at the insertion of the pulmonary veins. We will model the heterogeneities specific to the atria, like fibrosis or fatty infiltration. They are supposed to play a major role in the development of atrial fibrillation.

At the ventricular level, we focus on (1) modeling the complex coupling between the Purkinje network and the ventricles and (2) modeling the heteogeneities related to the complex organization and disorganization of the myocytes and fibroblasts. Point (1) is supposed to play a major role in sudden cardiac death and point (2) is important in the study of infarct scars for instance.

4.3. Clinical electrophysiology

Treatment of cardiac arrhythmia is possible by pharmacological means, by implantation of pacemakers and defibrillators, and by curative ablation of diseased tissue by local heating or freezing. In particular the ablative therapies create challenges that can be addressed by numerical means. Cardiologists would like to know, preferably by noninvasive means, where an arrhythima originates and by what mechanism it is sustained.

We address this issue in the first place using inverse models, which attempt to estimate the cardiac activity from a (high-density) electrocardiogram. A new project aims at performing this estimation on-site in the catheterization laboratory and presenting the results, together with the cardiac anatomy, on the screen that the cardiologist uses to monitor the catheter positions.

An important prerequisite for this kind of interventions and for inverse modeling is the creation of anatomical models from imaging data. The Carmen team contributes to better and more efficient segmentation and meshing through the IDAM project (section 6.2).

DRACULA Project-Team

4. Application Domains

4.1. Normal hematopoiesis

4.1.1. Introduction

Modelling normal hematopoiesis will allow us to explore the dynamical appearance of the various cell types, originating from the stem cell compartment, through the bone marrow development up to the blood stream. The differentiated cell types will both fulfill physiological functions, and play a key role on the feedback control on homeostasis (balance of the system) in their own lineages. We will describe the hematopoiesis from three different points of view:

- The initial cell type, the hematopoietic stem cell (HSC);
- The lineage choice question;
- Three differentiated lineages that are responsible for specific function, namely oxygen transport, immune response and coagulation.

The basic mechanisms of our modelling approach are as follows:

- Any cell type can have two possibilities at each time step: to divide or to die.
- At any division step, the cell can either give rise to two daughter cells which are identical to the mother cell (self-renewal) or that are more advanced in their differentiation.

All these processes will be first modelled at the cellular level. In parallel, we will develop models of intra-cellular molecular networks (as some proteins controlling the cell cycle) influencing this decision making process, so as to be able to describe both micro-to-macro effects (molecules influencing the global cell behaviour) as well as macro-to-micro effects (like the global state of the cell population influencing the molecular behaviour).

4.1.2. Hematopoietic stem cells (HSC)

Although widely studied by biologists, HSC are still poorly understood and many questions remain open: How fast and how frequently do they divide? How many of them are in the bone marrow and where? How is their behaviour modified under stress conditions such as blood loss or transfusion?

Our modelling approach will be based on two methods: deterministic and stochastic differential equations with delays (discrete and distributed), on one hand, and the DPD method using the individual based modelling on the other hand. The differential equation models based on the work initiated by Mackey [39] will describe the HSC compartment in normal conditions and the behaviour of these cells under some stress. The DPD method, as a complementary approach, will emphasize the spatial regulation of stem cell behaviour, and we will focus our attention to give a possible answer regarding their location in the bone marrow and the roles of the niche, their number in the system, their possible role under stress (that is their reaction under the different feedback controls).

4.1.3. Blood cell functions

(i) O2 transport: red lineage

O_2 transport is provided by red blood cells (RBC) also called erythrocytes. Many different stages of maturity (including progenitors, precursors, reticulocytes and erythrocytes) are necessary to achieve the complete formation of RBC. These latter are then released in the blood stream where they transport oxygen. The whole process is tightly dependent on a robust well-balanced equilibrium called homeostasis.

It has been shown in the 1990's that apoptosis is regulated by EPO, a growth factor released by the kidneys under hypoxia. But also, under severe stress (like an important blood loss) some other molecules known as glucocorticoids can be released leading to an increase of the self-renewing rate for each generation. This led to the formulation of a first model, demonstrating the role of self-renewal.

The study of the red blood cell lineage will involve different scale levels, from the molecular one, with the effects of the hormones on the surface and internal parts of the cell, the cell contacts in each stage of RBC formation, and the red branch population in its whole with all the interactions taken into account (see Figure 3) in normal and stress conditions.

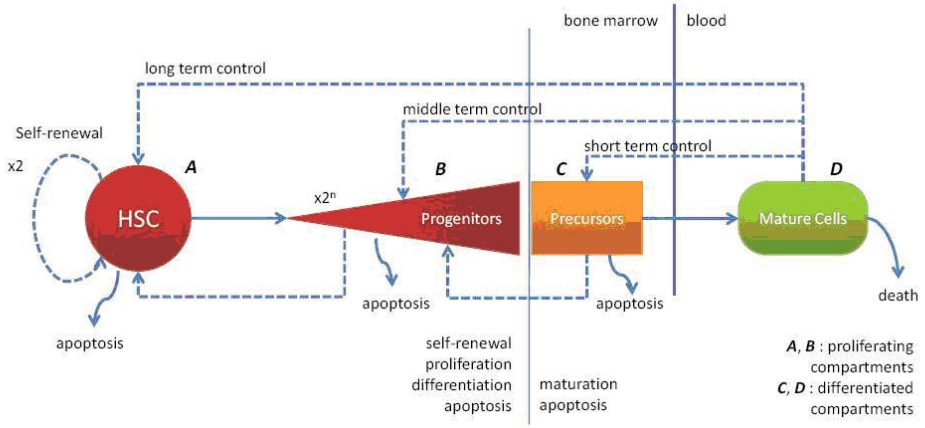

Figure 3. Scheme of Erythropoiesis Modelling ([27]). Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) or almost mature (precursors) cells, precursors may act on progenitor dynamics, etc..

In order to couple the cellular behaviour to explicit molecular events, we will describe the events through a molecular network that is based upon the work of [44]. A first version of this model is shown in Figure 2 .

(ii) Immune response

We will focus on the production of T-cells during an immune response. This represents an important activity of the lymphoid branch, part of leucopoiesis (white blood cell production). Several models of the myeloid branch of leucopoiesis have been investigated in the frame of specific diseases (for instance cyclical neutropenia ([38], [32]), chronic myelogenous leukemia [40]).

Time evolution of T-cell counts during an infection is well known: following the antigen presentation, the number of cells quickly increases (expansion), then decreases more slowly (contraction) and stabilizes around a value higher than the initial value. Memory cells have been produced, and will allow a faster response when encountering the antigen for a second time. Mechanisms that regulate this behaviour are however not well known.

A recent collaboration just started with immunologists (J. Marvel, Ch. Arpin) from the INSERM U851 in Lyon, who provide experimental data that are essential to assess the significance of models, based on strongly nonlinear ordinary differential equations, that can be proposed for T-cell production (Figure 4). By considering molecular events leading to cell activation when encountering a virus, we will propose a multi-scale model of the immune response.

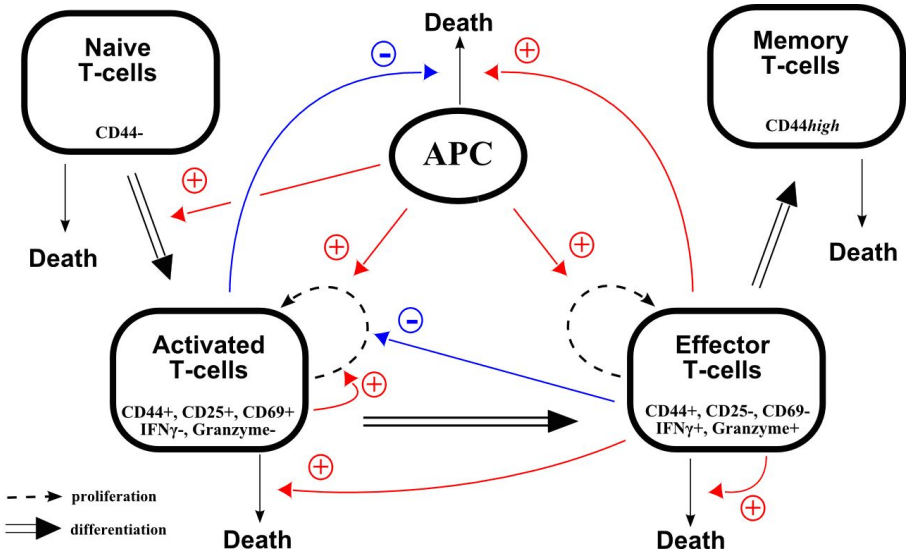

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naive T-cells. These latter, once activated, differentiate into activated cells which, under specific feedback loops will either die, differentiate into effector cells or self-renew. Differentiation of effector cells (killer cells) will result in the production of memory cells.

(iii) Coagulation: platelet lineage

Thrombopoiesis, the process of production and regulation of platelets, is similar to erythropoiesis although important differences are observed. These two processes have an immature progenitor (MEP) in common. Platelets are involved in blood coagulation, and can be the source of blood diseases (thrombopenia, thrombocytosis). Their production is mainly regulated by thrombopoietin (TPO), a growth factor similar to EPO.

It is important to mention that very few experimental data exist in the literature, and mathematical modelling of thrombopoiesis did not attract so much attention in the past 20 years. However, collaboration with some leading hematologists in this domain will allow us to get updated and new data regarding this process.

Deterministic models, in the form of structured transport partial differential equations, will be proposed to describe platelet dynamics, through the description of HSC, megakaryocytic progenitor and megacaryocyte (platelet precursor) compartments. Circulating TPO, regulated by platelets, will induce feedback loops in thrombopoiesis, and we will investigate the dynamics of platelet production and emergence of platelet-related diseases.

4.2. Pathological hematopoiesis

The knowledge of hematopoiesis and related diseases has evolved to become a great deal in the past years, and Mackey's previous models (ref. [30]) do not allow us to correctly answer current questions that are clearly oriented toward the investigation of cell signalling pathways. These models nevertheless bring relevant ideas about the essential features of such modelling. It is also noteworthy that even though models of hematopoiesis have existed for quite a long time, their application to questions of explanation and prediction of hematopoiesis dynamics that are encountered in the clinic is still not sufficiently frequent, even though much progress has been achieved in the cooperation between hematologists and mathematicians [41]. This is in the optic of testable experimental predictions that the multi-scale model for pathological hematopoiesis will be developed. For instance, we will concentrate on myeloid leukemias (CML and AML) and their treatment.

4.2.1. Leukemia Modelling

(i) Chronic Myeloid Leukemia

The strong tyrosine kinase activity of the BCR-ABL protein is the basis for the main cell effects that are observed in CML: significant proliferation, anti-apoptotic effect, disruption of stroma adhesion properties, genomic instability. This explains the presence in CML blood of a very important number of cells belonging to the myeloid lineage, at all stages of maturation.

We will consider models based on ordinary differential equations for the action of the main intra- and extracellular proteins involved in CML (as BCR-ABL protein), and of transport equations (with or without delay, physiologically structured or not to represent healthy and leukemic cell populations, take into account many interactions between proteins (especially BCR-ABL), cells (anti-apoptotic effect, etc.), and their environment (disruption of stroma adhesion properties, for example). Transport pertains thus to cells from one compartment (or a group of compartments) to another compartment, with a determined speed of aging or maturation. These compartments may be detailed or not: the less mature are stem cells, then progenitor cells, etc.

(ii) Acute Myeloid Leukemia

The natural history of CML leads to its transformation ("blast crisis") in acute myeloid leukemia (AML), following supplementary genetic alterations that produce a maturation arrest (myeloid in $3/4$ of cases, lymphoid in $1/4$ of cases, confirming the insult to pluripotent stem cells), leading to an accumulation of immature cells in the bone marrow and in the general circulation, resulting in deep medullary impairment and fast fatal outcome, in spite of chemotherapy. This phenomenon is the same as the one observed in de novo AML, i.e., AML without a previous chronic phase.

The different modelling methods of AML will be similar to the ones described for CML, with some exceptions: the appearance of BCR-ABL mutations, which are not relevant in the case of AML, the appearance of a gene (spi-1) involved in the differentiation arrest, and constitutive activation of EPO receptor or Kit activating mutations promote proliferation and survival. This explains the accumulation of immature cells in the bone marrow and in the blood stream.

4.2.2. Treatment

As far as treatment of pathological hematopoiesis is concerned, two main strategies currently exist that aim at slowing down or eliminating damaged cell proliferation. The first of these strategies consists in launching the apoptotic process during the cell division cycle. This process is activated, for example when the cell is unable to repair damages, e.g., after exposure to cytostatic drugs. A typical example is apoptosis induced by chemotherapy-induced DNA damage: The damage is recognised by the cell, which then activates the sentinel protein p53 ("guardian of the genome") that arrests the cell cycle to allow, if possible, damage repair. If the latter is unrecoverable, then p53 activates the endogenous apoptotic processes.

The second strategy aims at pushing damaged cells toward the differentiation that has been stopped in the course of their genetic mutation. Since a few years back, a new approach has been developed around the strategy of differentiation therapy. This therapy relies on molecules (growth factors and specific cytokines) that are able to re-initialise the cell differentiation programs that have been modified during malignant transformation. The cancer that is most concerned by the development of this differentiation therapy is AML whose malignant cells present highly undifferentiated features and the ones that present a translocation responsible for the differentiation (PML/RAR of the promyelocytic form, AML1/ETO and CBFbeta/MyH11, involving Core Binding Factors alpha and beta).

Mathematical models based on ordinary differential equations will be developed to describe the action of drugs (in the two cases mentioned above). They will take into account interactions between drugs and their environment. Our goal will be the optimization of possible synergies between drugs acting on distinct cellular targets, and the control of resistances to these treatments as well as their toxicities.

Curative and palliative strategies must take into account the dynamics of healthy and leukemic hematopoietic cells at multiple scales. In time, from optimal scheduling of combination therapy (hours) to avoiding the development of resistances and relapse (months to years). In space, from the stem cell niche to circulating blood. In organization, from gene and signalling networks (JAK/STAT, BCR-ABL) to cell populations and cytokine regulation (EPO, CSFs). Several recent qualitative models have provided insight in the complex dynamics of the disease and the response to treatments. Many of these models focus on the control or regulation processes that promote homeostasis or oscillatory behavior in cell number. However, as A. Morley points out, "once the control-systems features of hematopoiesis are accepted, the ability to construct a model that shows oscillatory behavior, even if the model incorporates the latest advances in hematopoietic cell biology, really adds little new knowledge. Rather, the challenge to modellers would seem to be to provide detailed predictions for the input-output characteristics of the different parts of the various control systems so that these predictions can be tested by experimental hematologists and a truly quantitative description of hematopoiesis can emerge".

We propose for instance, to use models in the form of structured transport partial differential equations (with or without delay, physiologically structured or not) to represent the competition between target, resistant and healthy cell populations. The resulting models to describe the dynamic of these cell populations under the action of drugs are multi-scale systems of the form (Hyperbolic PDE)-ODE or DDE-ODE. For instance, we will develop mathematical models of chronotherapy and pharmacotherapy for CML and AML.

M3DISIM Project-Team

4. Application Domains

4.1. Clinical applications

After several validation steps – based on clinical and experimental data – we have reached the point of having validated the heart model in a pre-clinical context where we have combined direct and inverse modeling in order to bring predictive answers on specific patient states. For example, we have demonstrated the predictive ability of our model to set up pacemaker devices for a specific patient in cardiac resynchronization therapies, see [10]. We have also used our parametric estimation procedure to provide a quantitative characterization of an infarct in a clinical experiment performed with pigs, see [1].

MAMBA Project-Team

4. Application Domains

4.1. Cancer modelling

Evolution of healthy or cancer cell populations under environmental pressure; drug resistance. Considering cancer as an *evolutionary disease*, evolution meaning here Darwinian evolution, but also Lamarckian instruction, of populations structured according to phenotypes relevant to describe their heterogeneity at stake in studies led in collaboration with our biologist partners within the Institut Universitaire de Cancérologie (IUC) of UPMC, we tackle the problem of understanding and limiting: a) the evolution from pre-malignancy to malignancy in cell populations (in particular we study early leukaemogenesis, leading to acute myeloid leukaemia), and b) in established cancer cell populations, the evolution towards drug-induced drug resistance. The environmental pressure guiding evolution has many sources, including signalling molecules induced by the peritumoral stroma (e.g., between a breast tumour and its adipocytic stroma), and anticancer drugs and their effects on both the tumour and its stromal environment. The models we use [63], [79], [80], [81] are close to models used in ecology for adaptive dynamics.

Drugs: pharmacokinetics-pharmacodynamics, therapy optimisation. We focus on multi-drug multi-targeted anticancer therapies aiming at finding combinations of drugs that theoretically minimise cancer cell population growth with the constraint of limiting unwanted toxic side effects under an absolute threshold (this is not L^2 nor L^1, but L^∞ optimisation, i.e. the constraints as well as the objective function are L^∞) in healthy cell populations and avoiding the emergence of resistant cell clones in cancer cell populations [59], [80], [60], [79]. Prior to using optimisation methods, we design models of the targeted cell populations (healthy and tumour, including molecular or functional drug targets [58]) by PDEs or agent-based models [56], and molecular pharmacological (pharmacokinetic-pharmacodynamic, PK-PD) models of the fate and effects in the organism of the drugs used, usually by ODE models. A special aspect of such modelling is the representation of multi-cellular spatio-temporal patterns emerging from therapies.

Multi-scale modelling of cancer invasion. The major step from a benign tumour to an invasive cancer is the development step at which cells detach from the tumour mass and invade individually the surrounding tissue [0]. We performed *in vitro* simulations of cancer cell invasion for breast cancer evaluating under which conditions the observed migration pattern occurs. (In collaboration with our biologist partners within the Institut Curie)

4.2. Modelling and control in epidemiology

The spread of certain strains of the intracellular parasitic bacterium *Wolbachia* in populations of mosquitoes *Aedes aegypti* drastically reduces their competence as vector of dengue and other severe mosquito-borne viral diseases known as arboviral infections (chikungunya, Zika, yellow fever...). In absence of vaccine, or of preventive or curative treatment, the release of mosquitoes infected by this bacterium has been recently considered a promising tool to control these diseases.

Technically the situation can be described by a bistable model, and the issue consists in moving from a Wolbachia-free equilibrium to a fully contaminated equilibrium. Therefore mathematical modeling is of great interest for the study of the feasibility of the control of dengue fever using this strategy.

Key questions about this method concern the efficacy of the strategies used to release Wolbachia-infected mosquitoes in the field that can be applied successfully and with limited cost.

[0] Weinberg, The biology of cancer, Garland, 2007

4.3. Protein polymerisation

Self-assembly of proteins into amyloid aggregates is an important biological phenomenon associated with various human neurodegenerative diseases such as Alzheimer's, Parkinson's, Prion (in particular variant Creutzfeldt-Jakob disease, epidemically linked to bovine spongiform encephalopathy, or so-called "mad cow", disease), Huntington's disease. Amyloid fibrils also have potential applications in nano-engineering of biomaterials.

However, the mechanisms of polymerisation are far from being quantitatively understood by biologists. They can be modelled with the help of coagulation-fragmentation equations, a field of expertise of MAMBA [16], [36], or with stochastic models [20]. One difficulty of this application is that the reactions imply both very small and very large scales for the sizes of polymers [7], experimental data giving only access to the time evolution of size-averaged quantities [6]. Moreover, there exists an intrinsic variability among experiments, which has to be distinguished from a lack of reproducibility [20].

The European starting grant SKIPPER^{AD} involves a long-term collaboration with Human Rezaei's team, a biologist expert group in amyloid diseases at INRA Jouy-en-Josas. It allowed us to further develop new collaborations, in particular with Wei-Feng Xue's team in Canterbury, who is one of the rare biophysicists in this area who is able to measure not only size-averaged quantities, as for instance the time-evolution of the total polymerised mass, but also size distribution of polymers (at least over a certain threshold). Such measurements allow us to use much more powerful inverse problems and data assimilation methods [6].

Moreover, this field of applications to human neurogenerative diseases brings us new questions [17], which is a stimulation for our mathematical research and at the same time allows us to provide biologists with a new and efficient tool.

4.4. Cell motion

Several processes are employed by cells to communicate, regulate and control their movements, and generate collective motion. Among them, chemotaxis is the phenomenon by which cells direct their active motion in response to an external chemical (or physical) agent. In chemotaxis, cells not only respond but can also produce the chemical agent, leading to a feedback loop. Understanding this phenomenon is a major challenge for describing the collective behaviour of cells. Many mathematical models have been proposed at different scales, yielding a good description of cell aggregation. In particular, mathematical models at macroscopic scale may be derived departing from kinetic description at mesoscopic scale. An interesting study at the numerical level is to provide numerical schemes able to treat both scales. Then in [27], we have proposed an asymptotic preserving scheme for a model describing the formation of networks of cells in tissues. In collaboration with biophysicists at Institut Curie in Paris, we develop and study [0] mathematical models based on kinetic equations for bacterial travelling waves in a microchannel. These models have shown a remarkable quantitative agreement with experimental observations. In [18], we extend this approach to study the behavior of the interaction between two populations of E. Coli. We show that in certain cases populations that travel with its own speed in the channel when separated, may synchronise their movements when put together.

Cell motion arises also in the growth of solid tumours, which can be described through cell population models or multiphase flows [0]. This is a very active subject because several bio-chemico-physical mechanisms are at work; for instance motion can arise from pressure forces resulting from cell divisions and from active cell motility. At the smaller scale stochastic agent-based models of tumour cells invading the tumour environment or blood vessels are considered [0], and allow to represent detailed behaviours and interactions. At a larger scale, free boundary problems are widely used, e.g., for image-based prediction because of the reduced number of parameters [0]. Asymptotic analysis makes a link between these different mechanistic models [88]. One other

[0] N. Bournaveas, V. Calvez, S. Gutiérrez and B. Perthame, Global existence for a kinetic model of chemotaxis via dispersion and Strichartz estimates, *Comm. PDE*, 2008

[0] J. Ranft et al, Fluidisation of tissues by cell division and apoptosis, *PNAS*, 2010 and L. Preziosi and A. Tosin, Multiphase modelling of tumour growth and extracellular matrix interaction: mathematical tools and applications, *J. Math. Biol.*, 2009.

[0] I. Ramis-Conde et al., J. Phys. Biol., 2009

[0] Works by O. Saut, T. Colin, A. Iollo, N. Ayache, J. Lowengrub

setting where we will study cell motion is 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 [86], [90] 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 settings, indicating the existence of conserved mechanisms that should be widespread across living beings. In the 01365414 thesis of Telmo Pereira, some differences between the two settings are also studied.

4.5. Physics of tissue organisation

Many new insights in the last years indicate that migration, growth and division of cells are largely impacted by cell and tissue mechanics [0], [0], [0]. Centre-based growth models already account for many of the observed phenomena [0], [0]. They furthermore allow calculation of the stress tensor in the tissue. A critical shortcoming of centre-based models is that forces between cells are calculated based on pairwise interactions hence multi-cellular interactions leading to true cell compression cannot be taken into account.
In order to scope with this shortcoming we (1.) developed a strategy in which forces are calibrated with a high resolution agent based model (so called deformable cell model), so that stress in tissue can then be calculated also at high cell density [54]; (2.) integrated cell division in deformable cell models to permit direct simulations of phenomena with this model type; (3.) developed hybrid models permitting to simulate centre-based and deformable cell models in the same simulations to be able to reach sufficiently high cell numbers.
Deformable cell models [0] resolve cell surface at reasonable resolution, and allow to calculate cell deformation as function of stress emerging in the tissue, hence the stress tensor cannot only be resolved at the position of the cell centre, as in the case of centre-based models, but in this case at any point on the cell surface or inside the cell. The higher resolution causes much longer simulation times which is why currently simulation of large multi-cellular systems with deformable cell models on standard computers is not feasible.

4.6. Liver modelling

Liver is the main detoxifying organ of the human body and can regenerate up to about 70% of its mass. It performs its task by using a complex tissue architecture, with hepatocytes aligning along micro-capillaries and forming a dense network. The incidence rate of liver diseases is steadily increasing, liver cancer ranking 6th among all cancers. About one person in 12, otherwise said 500 million people worldwide, will suffer from viral hepatitis. Hepatitis B and C as well as misuse of drugs or alcohol are major causes of liver cancer. Notwithstanding the importance of this public health problem, disease pathogenesis and regeneration in liver are still not well understood.
So far systems biology approaches addressing the tissue scale are rare. Most of those which do so base on compartment models (e.g. [0]); only recently are approaches addressing the tissue scale being developed [76] [0], [0], [0], [0]. We have developed a multi-scale model of liver regeneration representing the tissue architecture, the different cell types, the flow systems, hepatocyte metabolism and signal transduction controlling cell cycle entrance in the regeneration processes, taking into account extrahepatic compartments when relevant. Applications are regeneration after drug-induced damage and after partial hepatectomy, drug pharmacodynamics and

[0] Ingber, Proc. Natl. Acad. Sci (USA), 2005
[0] Trepat et. al., Nat. Phys. 2009
[0] Alessandri et. al., Proc. Natl. Acad. Sci. (USA) 2013
[0] Drasdo and Hoehme, Phys. Biol. 2005
[0] Drasdo and Hoehme, New Journal of Physics 2012
[0] Odenthal, Smeets, van Liedekerke, et. al., PloS Comput Biol. 2013
[0] Diaz-Ochoa et. al. Frontiers in Pharmacology, 2013
[0] Ricken, Dahmen, Dirsch, Biomech. Model. Mechanobiol. 2010
[0] Debbaut et. al., J. Biomech. Eng. 2014
[0] Siggers, Leungchavphongse, Ho, Repetto, Biomech. Model. Mechanobiol. 2014
[0] Schwen et. al., PLoS Comput. Biol. 2014

pharmacokinetics in liver and liver cancer, and model-based prediction of in-vivo drug toxicity from in-vitro measurements [0].

[0] Godoy et al., *Arch Toxicol. 2013* Aug;87(8):1315-1530

MONC Project-Team

4. Application Domains

4.1. Tumor growth monitoring and therapeutic evaluation

Each type of cancer is different and requires an adequate model. More specifically, we are currently working on the following diseases:

- Glioma (brain tumors),
- Meningioma (intracranial tumors),
- Metastases to the lung, liver from various organs,
- Soft-tissue sarcoma,
- Hepatocellular Carcinoma (primary liver tumors),

with starting works on kidney cancer, EGFR-mutated lung cancer and pancreas cancer.

In this context our application domains are

- Image-driven patient-specific simulations of tumor growth and treatments,
- Parameter estimation and data assimilation of medical images.

4.2. Biophysical therapies

- Modeling of electrochemotherapy on biological and clinical scales.
- Evaluation of radiotherapy and radiofrequency ablation.

4.3. In-vitro and animals experimentations in oncology

- Theoretical biology of the metastatic process: dynamics of a population of tumors in mutual interactions, dormancy, pre-metastatic and metastatic niche, quantification of metastatic potential and differential effects of anti-angiogenic therapies on primary tumor and metastases.
- Mathematical models for preclinical cancer research: description and prediction of tumor growth and metastatic development, effect of anti-cancerous therapies.

MYCENAE Project-Team

4. Application Domains

4.1. Introduction

MYCENAE addresses rather "upstream" questions in neuroendocrinology and neuroscience. Nevertheless, MYCENAE's expected results can contribute to more applied issues in these fields, mainly by helping understand the mechanisms underlying physiological and pathological processes and also by designing new concepts for biomedical data analysis. MYCENAE thematics are related to societal issues concerning endocrine disruptors, reproductive biotechnologies, and neurological diseases, especially in case of pathological synchronizations encountered in epilepsy and Parkinson's disease.

4.2. Neuroendocrinology and Neuroscience

We are interested in the complex dynamical processes arising within neuroendocrine axes, with a special focus on the reproductive (hypothalamo-pituitary-gonadal) axis. This axis can be considered as the paragon of neuroendocrine axes, since it both concentrates all remarkable dynamics that can be exhibited by these axes and owns its unique specificities, as gonads are the only organs that host germ cells. Since, in neuroendocrine axes, neural systems are embedded within endocrine feedback loops and interact with peripheral organs, one also needs to get interested in the peripheral dynamics to be able to "close the loop" and account for the effect of peripheral inputs on neural dynamics. In the case of the HPG axis, these dynamics are especially complex, because they involve developmental processes that occur even in adult organisms and combine the glandular function of the gonads with their gametogenic function.

Neuroendocrinology is thus a scientific field at the interface between Neuroscience, Endocrinology and Physiology (and even of Developmental Biology in the case of the HPG axis). On a neuroscience ground, mathematical neuroendocrinology is specifically interested in endocrine neurons, which have the uncommon ability of secreting neurohormones into the blood stream. Neuroendocrine networks are characterized by the emergence of very slow rhythms (on the order of an hour), finite size effects due to their relative small number of neurons (on the order of a few thousands for the Gonadotropin-Releasing-Hormone network) and neuroanatomical particularities, that impact the way they can synchronize and desynchronize. On a physiological ground, gonadal cell biology raises specific cell biology issues on more than one account. First, the gonads are the only organs sheltering the germ cell lines (corresponding to oogenesis in ovaries and spermatogenesis in testes). Hence, the two modes of cell division, mitosis and meiosis are encountered in these tissues. Second, there are intricate interactions between the gonadal somatic cells (granulosa cells in the ovaries, sertoli cells in the testes) and the germ cells. Third, the control of gonadal cell populations is exerted within endocrine feedback loops involving both the hypothalamus and pituitary, which results naturally in multiscale population dynamics coupled with hormonally-controlled cell kinetics.

MYCENAE's research topics in mathematical neuroscience deal with complex oscillations, synchronization and plasticity.

We study (i) the emergence of network-level behaviors from individual dynamics of excitable cells (mainly neurons, but not exclusively, as the pituitary cells belong to the family of excitable cells): complete synchronization or synchronization of specific events, effect of the recruitment rate in the synchronization process, dependence on the neuro-anatomical and functional coupling properties; (ii) the control of the different possible configurations of the network depending on external (e.g. daylength) and/or internal inputs (e.g. metabolic status), at the source of plasticity processes in cognitive (vision learning) or neuroendocrine systems (differential sensitivity to gonadal steroids and peptides across the different steps of the reproductive life); (iii) the encoding of neuro-hormonal signals as complex oscillations, on the electrical, ionic (calcium dynamics) and secretory levels; and (iv) the decoding of these signals by their target neuronal or non-neuronal cells.

More recently, we have been interested into developmental biology issues in neurosciences: neurogenesis and brain development. The anatomical and functional organization of the nervous system, and especially the brain, is highly structured and tightly regulated. The surface of the cortex, its thickness, but also the size and shape of the brain areas associated to the different sensory or motor areas are very reliable quantities across different individuals. In collaboration with different teams of biologists, we develop and investigate models of the development of the brain, at different time and spatial scale.

The biological relevance of our modeling and model-based signal analysis approaches is grounded on our network of collaborations with teams of experimentalist biologists. In particular, we have long standing collaborations with the UMR 6175 (INRA-CNRS-Université François Rabelais-Haras Nationaux) "Physiologie de la Reproduction et des Comportements" that covers most our research topics in reproductive neuroendocrinology. We have especially close links with the Bingo (Integrative Biology of the ovary) and Bios (Biology and Bioinformatics of Signaling Systems) teams, which were partners of the REGATE LSIA. We have been jointly investigating issues relative to terminal or basal follicular development [6], [7], analysis of neurosecretory patterns [15] and modeling of GPCR (G-Protein Coupled Receptors) signaling networks [9]. We also have special links with the Center for Interdisciplinary Research in Biology (CIRB, Collège de France), headed by Alain Prochiantz, that help us get a better understanding of how the brain connectivity develops and how it is functionally organized. An instance of a recent collaborative work is the study of the organization of spatial frequencies in the primary visual cortex [36].

NUMED Project-Team (section vide)

REO Project-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 though 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.* [58], [62], [61] 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/M3DISIM 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.