RESEARCH CENTER

FIELD
Digital Health, Biology and Earth

Activity Report 2014

Section Application Domains

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COMPUTATIONAL BIOLOGY

COMPUTATIONAL NEUROSCIENCE AND MEDECINE

EARTH, ENVIRONMENTAL AND ENERGY SCIENCES

MODELING AND CONTROL FOR LIFE SCIENCES

ABS Project-Team (section vide)

AMIB Project-Team (section vide)

BAMBOO Project-Team

4. Application Domains

4.1. Domain

The main area of application of BAMBOO is biology, with a special focus on symbiosis (ERC project) and on intracellular interactions.

BEAGLE Project-Team (section vide)

BIGS Project-Team (section vide)

BONSAI Project-Team

4. Application Domains

4.1. Sequence processing for Next Generation Sequencing

As said in the introduction of this document, biological sequence analysis is a foundation subject for the team. In the last years, sequencing techniques have experienced remarkable advances with Next Generation Sequencing (NGS), that allow for fast and low-cost acquisition of huge amounts of sequence data, and outperforms conventional sequencing methods. These technologies can apply to genomics, with DNA sequencing, as well as to transcriptomics, with RNA sequencing. They promise to address a broad range of applications including: Comparative genomics, individual genomics, high-throughput SNP detection, identifying small RNAs, identifying mutant genes in disease pathways, profiling transcriptomes for organisms where little information is available, researching lowly expressed genes, studying the biodiversity in metagenomics. From a computational point of view, NGS gives rise to new problems and gives new insight on old problems by revisiting them: Accurate and efficient remapping, pre-assembling, fast and accurate search of non exact but quality labelled reads, functional annotation of reads, ...

4.2. Noncoding RNA

Our expertise in sequence analysis also applies to noncoding RNA. Noncoding RNA plays a key role in many cellular processes. First examples were given by microRNAs (miRNAs) that were initially found to regulate development in *C. elegans*, or small nucleolar RNAs (snoRNAs) that guide chemical modifications of other RNAs in mammals. Hundreds of miRNAs are estimated to be present in the human genome, and computational analysis suggests that more than 20% of human genes are regulated by miRNAs. To go further in this direction, the 2007 ENCODE Pilot Project provides convincing evidence that the Human genome is pervasively transcribed, and that a large part of this transcriptional output does not appear to encode proteins. All those observations open a universe of “RNA dark matter” that must be explored. From a combinatorial point of view, noncoding RNAs are complex objects. They are single stranded nucleic acid sequences that can fold forming long-range base pairings. This implies that RNA structures are usually modelled by complex combinatorial objects, such as ordered labeled trees, graphs or arc-annotated sequences.

4.3. Genome structures

Our third application domain is concerned with the structural organization of genomes. Genome rearrangements are able to change genome architecture by modifying the order of genes or genomic fragments. The first studies were based on linkage maps and fifteen year old mathematical models. But the usage of computational tools was still limited due to the lack of data. The increasing availability of complete and partial genomes now offers an unprecedented opportunity to analyse genome rearrangements in a systematic way and gives rise to a wide spectrum of problems: Taking into account several kinds of evolutionary events, looking for evolutionary paths conserving common structure of genomes, dealing with duplicated content, being able to analyse large sets of genomes even at the intraspecific level, computing ancestral genomes and paths transforming these genomes into several descendant genomes.

4.4. Nonribosomal peptides

Lastly, the team has been developing for several years a tight collaboration with Probiogem lab on nonribosomal peptides, and has became a leader on that topic. Nonribosomal peptide synthesis produces small peptides not going through the central dogma. As the name suggests, this synthesis uses neither messenger RNA nor ribosome but huge enzymatic complexes called nonribosomal peptide synthetases (NRPSs). This alternative pathway is found typically in bacteria and fungi. It has been described for the first time in the 70’s [14]. For the last decade, the interest in nonribosomal peptides and their synthetases has considerably increased, as witnessed by the growing number of publications in this field. These peptides are or can be used in many biotechnological and pharmaceutical applications (e.g. anti-tumors, antibiotics, immuno-modulators).

DYLISS Project-Team

4. Application Domains

4.1. Formal models in molecular biology

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.

Biological data integration. 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 implied 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 .

Asymptotic dynamics of a biological system 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 Pufa's are found to be produced using a set of pathways specific to brown algae, the work in axis 2 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 Pufa's 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 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 Pufa's controlling pathways have to be precisely identified. Actors structures are represented by syntactic models (see Fig. 4). 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.

4.2. Application fields

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 [22], [19]. 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 [28]. The same tool also allowed us to gain a better understanding of cyanobacteria proteins [2]. Finally, in dynamical systems, we use asymptotic analysis (tool *pogg*) to decipher the initiation of sea urchin translation [47]. We are currently initiating two new research programs in this domain: the team will participate to a collaboration program with the Biocore and Ange Inria teams, focused on the understanding on green micro-algae; and we will be involved in the deciphering of phytoplancton variability at the system biology level in collaboration with the Station Biologique de Roscoff.

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 *bioquali, ingranalysis, shogun, lombarde* were designed in this context [5]. In parallel, in collaboration with Ifremer (Brest), we have conducted similar work to decipher protein-protein interactions within archebacteria [55]. Our sequence analysis tool (*logol*) allowed us to build and maintain a very expressive CRISPR database [9] [27].

Similarly, in **animal biology**, our goal is to propose methods to identify regulators of very complex phenotypes related to nutritional issues. In collaboration with researchers from Inra/Pegase and Inra/Igeep laboratories, we develop methods to distinguish the response of cows, chicken or porks to different diaries or treatments and characterize upstream transcriptional regulators for such a response. The system biology tool *nutritional analyzer* was designed in this framework [14]. The pattern matching tool *logol* also allows for a fine identification of transcription factor motifs [51] [27]. Constraints-based programming also allows us to decipher regulators of reproduction for pea aphids [30], [13]. Semantic-based analysis was useful for interpreting differences of gene expression in pork meat [20].

We are less involved in **bio-medical applications** as the models and data studied in this application field are well informed and rather data-driven. 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 [46]. 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 [23] and N. Theret group at Inserm/Irset (Rennes) [15]. The dynamical system tools *caspo and cadbiom* were designed within these collaborations. Future studies will focus on the understanding of the metabolism of xenobiotics, still in collaboration with Inserm/Irset (Rennes).

GENSCALE Project-Team

4. Application Domains

4.1. Sequence comparison

Historically, sequence comparison has been one of the most important topics in bioinformatics. BLAST is a famous software tool particularly designed for solving problems related to sequence comparisons. Initially conceived to perform searches in databases, it has mostly been used as a general-purpose sequence comparison tool. Nowadays, together with the inflation of genomic data, other software comparison tools that are able to provide better quality solutions (w.r.t the ones provided by BLAST) have been developed. They generally target specific comparison demands, such as read mapping, bank-to-bank comparison, meta-genomic sample analysis, etc. Today, sequence comparison algorithms must clearly be revisited to scale up with the very large number of sequence objects that new NGS problems have to handle.

4.2. Genome comparison

This application domain aims at providing a global relationship between genomes. The problem lies in the different structures that genomes can have: segments of genome can be rearranged, duplicated or deleted (the alignment can no longer be done in one piece). Therefore one major aim is the study of chromosomal rearrangements, breaking points, structural variation between individuals of the same species, etc. However, even analyses focused on smaller variations such as Single Nucleotide Polymorphisms (SNP) at the whole genome scale are different from the sequence comparison problem, since one needs first to identify common (orthologous) parts between whole genome sequences and thus obtain this global relationship (or map) between genomes. New challenges in genome comparison are emerging with the evolution of sequencing techniques. Nowadays, they allow for comparing genomes at intra-species level, and to deal simultaneously with hundreds or thousands of complete genomes. New methods are needed to find the sequence and structural variants between such a large number of non-assembled genomes. Even for the comparison of more distant species, classical methods must be revisited to deal with the increasing number of genomes but more importantly their decreasing quality: genomes are no longer fully assembled nor annotated.

4.3. Protein comparison

Comparing protein is important for understanding their evolutionary relationships and for predicting their structures and their functions. While annotating functions for new proteins, such as those solved in structural genomics projects, protein structural alignment methods may be able to identify functionally related proteins when the sequence identity between a given query protein and the related proteins are low (i.e. lower than 20%). Moreover, protein comparison allows for solving the so-called protein family identification problem. Given an unclassified protein structure (query), the comparison of protein structures can be used for assigning a score measuring the "similarity" between the query and the proteins belonging to a set of families. Based on this score, the query is assigned to one of the families of the set. The knowledge acquired by performing such analyses can then be exploited in methods for protein structure prediction that are based on a homology modeling approach.

IBIS Project-Team (section vide)

LIFEWARE 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. Moreover, 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 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 vesicles

In collaboration with Franck Molina (CNRS, Sysdiag, 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 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 Sysdiag, 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 is also particularly appealing for security considerations in synthetic biology and compliance to forthcoming EU regulation.

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[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.

MAGNOME Project-Team

4. Application Domains

4.1. Function and history of genomes

Yeasts provide an ideal subject matter for the study of eukaryotic microorganisms. From an experimental standpoint, the yeast *Saccharomyces cerevisiae* is a model organism amenable to laboratory use and very widely exploited, resulting in an astonishing array of experimental results. From a genomic standpoint, yeasts from the hemiascomycete class provide a unique tool for studying eukaryotic genome evolution on a large scale. With their relatively small and compact genomes, yeasts offer a unique opportunity to explore eukaryotic genome evolution by comparative analysis of several species. MAGNOME applies its methods for comparative genomics and knowledge engineering to the yeasts through the ten-year old Génolevures program (GDR 2354 CNRS), devoted to large-scale comparisons of yeast genomes with the aim of addressing basic questions of molecular evolution.

We developed the software tools used by the CNRS's http://www.genolevures.org/ web site. For example, MAGNOME's Magus system for simultaneous genome annotation combines semi-supervised classification and rule-based inference in a collaborative web-based system that explicitly uses comparative genomics to simultaneously analyse groups of related genomes.

4.2. Alternative fuels and bioconversion

Oleaginous yeasts are capable of synthesizing lipids from different substrates other than glucose, and current research is attempting to understand this conversions with the goal of optimizing their throughput, production and quality. From a genomic standpoint the objective is to characterize genes involved in the biosynthesis of precursor molecules which will be transformed into fuels, which are thus not derived from petroleum. MAGNOME's focus is in acquiring genome sequences, predicting genes using models learned from genome comparison and sequencing of cDNA transcripts, and comparative annotation. Our overall goal is to define dynamic models that can be used to predict the behavior of modified strains and thus drive selection and genetic engineering.

4.3. Winemaking and improved strain selection

Yeasts and bacteria are essential for the winemaking process, and selection of strains based both on their efficiency and on the influence on the quality of wine is a subject of significant effort in the Aquitaine region. Unlike the species studied above, yeast and bacterial starters for winemaking cannot be genetically modified. In order to propose improved and more specialized starters, industrial producers use breeding and selection strategies.

Comparative genomics is a powerful tool for strain selection even when genetic engineering must be excluded. Large-scale comparison of the genomes of experimentally characterized strains can be used to identify quantitative trait loci, which can be used as markers in selective breeding strategies. Identifying individual SNPs and predicting their effect can lead to better understanding of the function of genes implicated in improved strain performance, particularly when those genes are naturally mutated or are the result of the transfer of genetic material from other strains. And understanding the combined effect of groups of genes or alleles can lead to insight in the phenomenon of heterosis.

4.4. Knowledge bases for molecular tools

Affinity binders are molecular tools for recognizing protein targets, that play a fundamental in proteomics and clinical diagnostics. Large catalogs of binders from competing technologies (antibodies, DNA/RNA aptamers, artificial scaffolds, etc.) and Europe has set itself the ambitious goal of establishing a comprehensive, characterized and standardized collection of specific binders directed against all individual human proteins, including variant forms and modifications. Despite the central importance of binders, they presently cover only a very small fraction of the proteome, and even though there are many antibodies against some targets (for example, > 900 antibodies against p53), there are none against the vast majority of proteins. Moreover, widely accepted standards for binder characterization are virtually nonexistent. Alongside the technical challenges in producing a comprehensive binder resource are significant logistical challenges, related to the variety of producers and the lack of reliable quality control mechanisms. As part of the ProteomeBinders and Affinomics projects, MAGNOME works to develop knowledge engineering techniques for storing, exploring, and exchanging experimental data used in affinity binder characterization.

MORPHEME Project-Team (section vide)

SERPICO Project-Team

4. Application Domains

4.1. Biological pilot models: Birbeck granule and Melanosome biogenesis

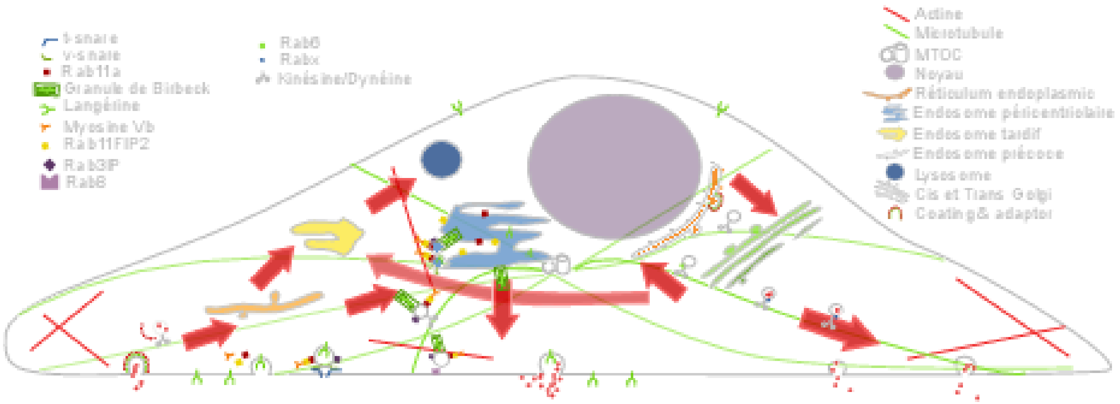

Figure 1. Cargo Langerin Trafficking controlled by Rab11A/Rab11FIP2/MyoVb platform.

In the past recent years, research carried at UMR 144 CNRS-Institut Curie ("Space Time imaging of Endomembranes and organelles Dynamics" (STED) 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.

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

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.

Clinical domain: Diagnosis of neurological disorder

- *Parkinson's and Alzheimer's diseases* are among the most important CNS diseases. Six million patients (among which 850.000 in France) are suffering from Alzheimer's, making it the most important neurodegenerative disease in Europe. Over 85 years of age, 1 woman in 4 and 1 man in 5 are affected in Europe. In France, the number of Alzheimer's patients is expected to reach at least 2 million in 2025 and will probably double in 2050, with the increasing age of the population. Parkinson's disease is the second most important neurodegenerative disease. There are six and a half million patients in the world and roughly 150.000 patients in France, among which 10% are under 40 and 50% over 58. Together with our partners from NeuroSpin (Saclay), Inserm U678 and CENIR (CHUPS, Paris), we are involved in the ANR project NucleiPark which is about high field MRI of the braintem, the deep nuclei and their connections in the Parkinsonian syndromes.
- *Spinal Cord Injury* (SCI) has a significant impact on the quality of life since it can lead to motor deficits (paralysis) and sensory deficits. In the world, about 2.5 million people live with SCI (http://www.campaignforcure.org). To date, there is no consensus for full rehabilitative cure in SCI, although many therapeutic approaches have shown benefits [77], [81]. It is thus of great importance to develop tools that will improve the characterization of spinal lesions as well as the integrity of remaining spinal tracts to eventually establish better prognosis after spinal injury. We have already started to be active in this domain with our collaborators at Inserm U678 (H. Benali) and CRSN/FacultÃ© de mÃ©decine UniversitÃ© de MontrÃ©al (Pr. S. Rossignol).

4.2. Applications of M/EEG

Applications of EEG and MEG cover: **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 are conducting a feasibility study with the Nice University Hospital on the usage of BCI-based communication for ALS [0] patients.

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

DEMAR Project-Team (section vide)

GALEN Project-Team

4. Application Domains

4.1. Brain Tumors and Neuro-degenerative diseases

The use of contrast enhanced imaging is investigated in collaboration with the Montpellier University Hospital towards better understanding of low-gliomas positioning, automatic tumor segmentation/identification and longitudinal (tumor) growth modeling. Furthermore, in collaboration with the Neurospin center of CEA and the Brookhaven National Laboratory at StonyBrook University we investigate the use of machine learning methods towards automatic interpretation of functional magnetic resonance imaging between cocaine addicted and normal subjects. Last, but not least in collaboration with the Georges Pompidou European Hospital an effort toward understanding tumor perfusion process through comportemental models is carried out with emphasis given on elastic organs.

4.2. Image-driven Radiotherapy Treatment & Surgery Guidance

The use of CT and MR imaging for cancer guidance treatment in collaboration with the Gustave Roussy Institute of Oncology. The aim is to provide tools for automatic dose estimation as well as off-line and online positioning guidance through deformable fusion between imaging data prior to each session and the ones used for scheduling/planning and dose estimation. The same concept will be explored in collaboration with the Saint-Antoine University Hospital towards image-driven surgery guidance through 2D to 3D registration between interventional and pre-operative annotated data.

4.3. Fundus Image Analysis

Retinal images–also known as fundus images or retinographies–are projective color im- ages of the inner surface of the human eye. In collaboration with Pladema Institute, UNCPBA, Argentina, we are developing a suite of software tools for automatic analysis of retinal images driven by statistical learning approaches.

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 subcortical 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.

NEUROMATHCOMP Project-Team (section vide)

NEUROSYS 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 anaesthesist in the control of the anaesthesia depths of patients during surgery. However, the conventional monitors exhibit a large variability between the patients detected anaesthetic depth and their real depth. 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 everyday. One reason for the lacking control of such disadvantagous 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 Frohlich, 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 un-controlled 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 anaesthesized 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 Wuerzburg. 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 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 wether the anesthezized patient feels pain and hence will develop cognitive impairement after surgery. Today, the anesthesiologist knows and detects physiological signs of pain, such as sweat, colour of skin or spontaneous unvoluntary 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. Human neuroimaging data and their use

Human neuroimaging consists in acquiring non-invasively image data from normal and diseased human populations. Magnetic Resonance Imaging (MRI) can be used to acquire information on brain structure and function at high spatial resolution.

- T1-weighted MRI is used to obtain a segmentation of the brain into different different tissues, such as gray matter, white matter, deep nuclei, cerebro-spinal fluid, at the millimeter or sub-millimeter resolution. This can then be used to derive geometric and anatomical information on the brain, e.g. cortical thickness.
- Diffusion-weighted MRI measures the local diffusion of water molecules in the brain at the resolution of 1 to 2mm, in a set of directions (60 typically). Local anisotropy, observed in white matter, yields a local model of fiber orientation that can be integrated into a geometric model of fiber tracts along which water diffusion occurs, and thus provides information on the connectivity structure of the brain.
- Functional MRI measures the blood-oxygen-level-dependent (BOLD) contrast that reflects neural activity in the brain, at a spatial resolution of 1.5 to 3mm, and a temporal resolution of about 2s. This yields a spatially resolved image of brain functional networks that can be modulated either by specific cognitive tasks or exhibit spontaneous co-activations.
- Electro- and Magneto-encephalography (MEEG) are two additional modalities that complement functional MRI, as they directly measure the electric and magnetic signals elicited by neural activity, at the millisecond scale. These modalities rely on surface measurements and do not localize brain activity very accurately in the spatial domain.

4.2. High-field MRI

High field MRI as performed at NeuroSpin (7T on humans, 11.7T in 2017, 17.6T on rats) brings an improvement over traditional MRI acquisitions at 1.5T or 3T, related to to a higher signal-to-noise ratio in the data. Depending on the data and applicative context, this gain in SNR can be traded against spatial resolution improvements, thus helping in getting more detailed views of brain structure and function. This comes at the risk of higher susceptibility distortions of the MRI scans and signal inhomogeneities, that need to be corrected for. Improvements at the acquisition level may come from the use of new coils (such as the 32 channels coil on the 7T at NeuroSpin), as well as the use of multi-band sequences [44].

4.3. Technical challenges for the analysis of neuroimaging data

The first limitation of Neuroimaging-based brain analysis is the limited Signal-to-Noise Ratio of the data. A particularly striking case if functional MRI, where only a fraction of the data is actually understood, and from which it is impossible to observe by eye the effect of neural activation on the raw data. Moreover, far from traditional i.i.d. Gaussian models, the noise in MRI typically exhibits local and long-distance correlations (e.g. motion-related signal) and has potentially large amplitude, which can make it hard to distinguish from true signal on a purely statistical basis. A related difficulty is the *lack of salient structure* in the data: it is hard to infer meaningful patterns (either through segmentation or factorization procedures) based on the data only. A typical case is the inference of brain networks from resting-state functional connectivity data.

Regarding statistical methodology, neuroimaging problems also suffer from the relative paucity of the data, i.e. the relatively small number of images available to learn brain features or models, e.g. with respect to the size of the images or the number of potential structures of interest. This leads to several kinds of difficulties, known either as *multiple comparison problems* or *curse of dimensionality*. One possibility to overcome this challenge is to increase the amount of data by using images from multiple acquisition centers, at the risk of introducing scanner-related variability, thus challenging the homogeneity of the data. This becomes an important concern with the advent of cross-modal neuroimaging-genetics studies.

POPIX Team

4. Application Domains

4.1. Pharmacometrics

Participants: Marc Lavielle, Kevin Bleakley, Célia Barthélémy.

POPIX is directly implicated in the domain of pharmacology. Historically, Marc Lavielle was the driving force behind the pharmacological modeling software MONOLIX, now an industry standard. Lixoft, an Inria start-up, now develops and supports MONOLIX and the commercial side of things. POPIX collaborates closely with Lixoft to transfer research results into software improvements and the development of new user tools in MONOLIX.

POPIX is also majorly implicated in the 5-year DDMoRe (Drug and Disease Model Resources) European project financed by the IMI (Innovative Medicines Initiative), a public-private partnership. In particular, POPIX has the task of developing new tools and methods for this project regrouping researchers in pharmacometrics, biostatistics and biology from both the public and private sectors. Specific tools and methods being developed by POPIX include:

- a clinical trial simulator
- protocol optimization tools
- diagnostic tools
- model selection tools
- data exploration tools
- estimation techniques for complex models (eg, stochastic differential equations, partial differential equations)

4.2. Gene expression

Participant: Marc Lavielle.

Mixed effects models can also be successfully used in quantitative biology for modeling the dynamics of biological networks in cell populations. Indeed, the population approach is relevant for building predictive computational models of intracellular processes. POPIX was interested with the experiments performed by the CONTRAINTES Inria team looking at the high-osmolarity glycerol (HOG) pathway in budding yeast. Yeast cells are exposed to osmotic shocks, i.e., sudden changes in the solute concentration of their surroundings. Signal transduction pathways, most notably the HOG pathway, provide information to the cell about the osmolarity of its environment and activate responses to deal with these stress conditions. In particular, a large set of genes is turned on and corresponding stress-responsive proteins are produced. This protein production process can be quantified by replacing one target protein, for example STL1, by a fluorescent protein such as yECitrine. This can be done by genetically modifying the yeast genome.

Thanks to time-lapse microscopy and cell tracking algorithms, single cell responses can be measured over time. Significant inter-cell variability is often observed.

The related Hog1-induced gene expression model is given by a parametric reaction network. MONOLIX can then be used to estimate the model parameters.

A collaboration with LIFEWARE (formerly CONTRAINTES) is starting on this subject.

4.3. Oncology

Participants: Marc Lavielle, Célia Barthélémy.

Despite great advances in the treatment and diagnosis of cancer, many steps remain to further improve prognoses and quality of life of cancer patients. Numerical models can be used to help adapt treatment protocol to the characteristics of each patient, ie, improve treatment efficacy by:

- choosing the best treatment
- choosing the best dose
- choosing the best drug-delivery protocol
- optimizing the above parameters to minimize toxicity

POPIX is part of the Inria project Lab MoNICa (MOdèles Numériques et Imagerie pour le CAncer), including the NUMED, MC2 and ASCLEPIOS Inria teams, that aims to optimize the parameters listed above using numerical modeling.

Collaborations with NUMED and MC2 are ongoing, with the aim of extending the statistical methods developed by POPIX to partial differential equation-based models. NUMED works on models of tumor growth and has previously implemented an extension of MONOLIX to KPP-type reaction-diffusion models.

4.4. Respiratory system

Participants: Bertrand Maury, Astrid Decoene.

Comprehensive models to simulate the whole pulmonary system, i.e., the mechanical behavior of the lung and gas exchanges within the pulmonary system, are built upon ODE and PDE approaches. For instance, the mechanical behavior of a lung is often described by single or multi-compartment ODE models, whereas air flow may be determined by the coupling of a 3D PDE system in the proximal part of the bronchial tree with a 0D ODE system in the distal part of the bronchial tree. Gas exchange has so far been investigated using 0D or 1D models in which heterogeneity of gas exchange along the path length may be investigated.

In a mathematical representation of such physiological systems, model parameters can be associated with specific quantities in the real system, such as the resistance and compliance of the pulmonary system. These quantities are time-dependent and nonlinear and are measured by pneumologists in order to characterize chronic obstructive pulmonary diseases (COPD) such as asthma and emphysema. These parameters may be useful in assessing lung conditions.

Although most physiological studies have used averaged deterministic models of the tracheobronchial tree geometry, morphometric studies show that inter-subject and intra-subject variability in the structural components of the human lung is significant. In particular, the resistance of the respiratory tract may be significantly affected as it is directly related to the inner diameter of the bronchi. Feedback from such variability to resistance and, as a consequence efficiency of the gas exchange process, within the framework of a fully coupled model, is unclear. In this situation, the statistical and numerical approaches being developed by POPIX are clearly promising estimation methods for respiratory system analysis.

4.5. Blood flow modeling

Participants: Bertrand Maury, Astrid Decoene.

Modeling and numerical simulation of blood flow in arteries and veins may become an important tool for medical applications, as for instance in the prediction of cardiovascular disease. Analyzing the pressure waves and estimating the wall compliance of arteries is fundamental, as these exhibit strong inter- and intra-subject variability. Currently, non-invasive pressure measurements involve excessive errors; intensive direct estimation is thus not applicable in practice. Physiologists therefore hope to be able to predict the time and space evolution of the pressure in the arterial network from a small amount of flow data measured at a few points.

Several numerical models have been developed in order to simulate blood flow in arteries and veins. They mainly consist of one to three-dimensional systems of partial differential equations, depending on the level of complexity one desires to achieve. Coupling the various models is also an issue. These numerical models allow us to compute the transversal section area, as well as the velocity or flow at different points in space, leading to a rather complete description of the arterial flow (velocity, pressure, section). But for these models to be adapted to each patient, certain numerical and physical parameters must be fitted, such as the compliance of walls and the viscosity of the blood. These parameters are difficult to estimate experimentally and may be related to measurements which involve a non-negligible error. Furthermore, their optimal value is linked to the particular modeling framework and therefore can differ from the value given by their physical definition.

Mixed models appear to be an appropriate framework for taking into account the specific nature of each patient and quantifying uncertainty in the numerical model. Flow data are available as it is possible to non-invasively measure the mean velocity in and diameter of an artery.

We aim to introduce statistical mixed models to the framework for the classical one-dimensional blood flow model.

SHACRA Project-Team (section vide)

SISTM 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" [44], "Systems medicine" [35]. 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) [34]. 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.

VISAGES Project-Team

4. Application Domains

4.1. Neuroimaging

neuroimaging, clinical neuroscience, multiple sclerosis, multispectral MRI, brain atlas

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 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.

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 quasi-steady state, which is the balance between the gravity and the Coriolis forces, can significantly improve the forecasts. In addition, the 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. Iy 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 the damages by means of suitable amenities. In France, floods are the most recurring natural disasters and produce the worse damages. In addition, it can be a cause or a consequence of a dam break. The large surface they cover and the long period they can last requires 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 required fluid/structure interactions to be well understood. Moreover, underground flows, in particular in sewer, 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 not the case close to the epicenter and in the coastal zone where the bathymetry leads a vertical accretion and produce substantial dispersive effects. The non-hydrostatic terms have to be considered and an efficient numerical resolution should be induced.

Whereas 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 CO_2 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 a kinetic and potential part. The buoys use the potential energy whereas the turbines (hydrolian) 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

4. Application Domains

4.1. Tokamaks

In the conception of the ITER tokamak, several key challenging points have been identified. One of them is the necessity to understand and control the huge thermal loads that are directed to the divertor target plates from the scrape-off layer (SOL) region since they are at the edge of or above what can be handled by today's materials. In the same spirit, the control of ELMs type instabilities that can also result in huge energy losses impacting the plasma facing components is considered as of crucial importance for the ITER program. The optimization of scenarii for designing the discharges of ITER and WEST will be addressed as well as some problems of ionospheric plasma.

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 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.

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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KALIFFE Project-Team

4. Application Domains

4.1. Plasma Physics and fusion energy

Taking into account spatial effects and time evolution of hot plasmas therefore leads to severe numerical challenges first on modeling aspects and second on purely numerical issues like oscillations and multiscale phenomena. Time scales are very different, ranging from pico-seconds to seconds. This requires special treatment to avoid excessive computing time, as for instance slow/fast manifold decomposition or time averaging. These two difficulties lead to the study and development of new robust numerical schemes and algorithms in order to preserve accuracy and stability within reasonable computing time. To speed up model development the use of refined numerical schemes must be as automatized as possible. Slow/fast manifold should be constructed automatically from the model, and spatial discretization should be as transparent as possible in order to apply former works (semi-Lagrangian or particle methods for transport, spectral or finite difference methods for collisions) on this topic.

Our program can be split into three different tasks :

- derivation of new collision operators based both on Coulombian interactions and strong external forces, approximation of collisional operators for multi-species by developing fast algorithms ;
- numerical treatment of multi-scale problems applying AP schemes to problems taking into account electromagnetic effects and collisions ;
- hybrid methods to take advantage of different regimes and reduce the computational cost.

Approximation of collision operators in plasma physics & conception of softwares for collisional plasmas.

An important step in the understanding of high temperature and dense plasmas is to investigate the effect of weakly Coulombian interactions, namely the Landau or Landau-Fokker-Planck collision operator. Due to the high temperature, collisions between particles have been neglected most of the time, but for the long time simulations, it seems that collisions may contribute and induce some nonlinear effects stabilizing the plasma. Furthermore, for inertial and magnetic confinement fusion, classical collision operators are no longer valid since their derivation, based on microscopic interactions only take into account self-interactions but no external forces, which are not negligible in our applications. There are only few works of physicists on this topic in 80's.

Then, our objective is to derive such operators to describe collisional plasmas and to simulate the transport of classical, as well as relativistic electrons, within a multi-species plasma, containing mobile electrons and ions. Issues to be addressed on this topic involve the derivation of multi-scale models due to different scales of effective constants, spatial heterogeneity and strength of boundary conditions.

Moreover, because of the quadratic aspect of the kernel and the multiple integrations in its analytical formulation, the Landau-Fokker-Planck equation is complicated to compute even if fast algorithm are available O($N \log N$), where N is the number of degree of freedom. Henceforth, different simpler models have been introduced, especially the BGK model which is mainly a relaxation towards a Maxwellian equilibrium state, or the linear Fokker-Planck which is a diffusive operator or a nonlinear Fokker-Planck operator taking into account Coulombian interactions. Although, these operators describes correctly the hydrodynamical limit, they usually do not give the correct transport coefficient in the Chapman-Enskog expansion. Our interest here is to compare the different operators in the description of binary collisions between ions-electrons or electrons-electrons and to select the one which is adapted with respect to the physical situation.

Collisional plasma and fluid models One characteristic of plasma physics problems is that they involve many different phenomena (instabilities, saturation phenomena due to nonlinear effects which couple different modes), many different time (plasma frequency, girokinetic frequency, etc) and space scales. Splitting a model in sub-models and studying their interactions is a central point, leading to new questions: how to define sub-models? How to simplify or complexify them?

For instance, the interaction of intense lasers with solid matter generates a hot plasma state that is well described by the Vlasov-Maxwell equation at the ignition point, whereas collective effects (electromagnetic fields) and collisions have to be taken into account around the impact and fluid models are sufficient in the capsule (see Figure 1). Accurate and efficient modeling of the physics in these scenarios is highly pertinent, because it relates to experimental campaigns to produce energy by inertial confinement fusion on facilities such as the Laser Méga-Joules in Bordeaux. Calculations involving the Vlasov-Fokker-Planck equation are computationally intensive, but are crucial to proper understanding of a wide variety of physical effects and instabilities in inertial fusion plasmas.

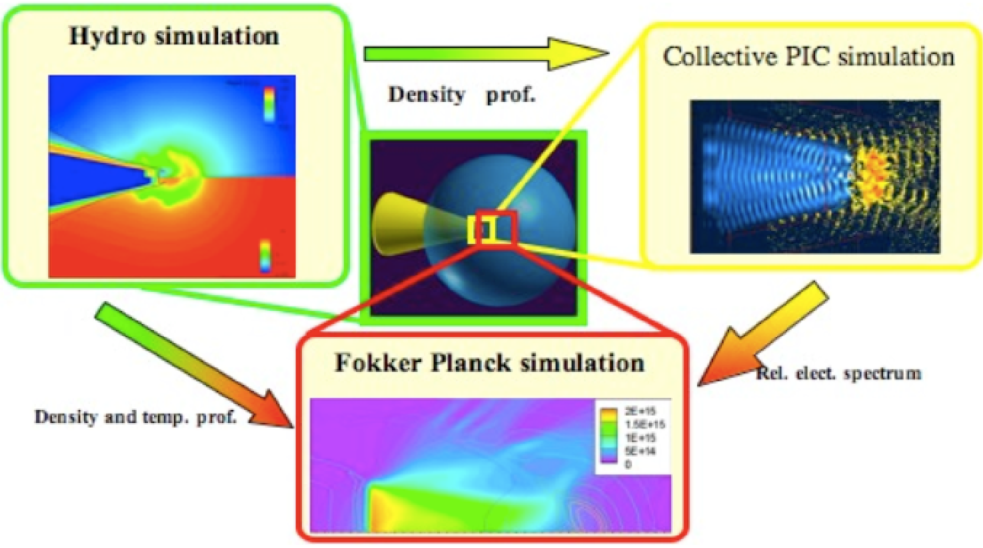

Figure 1. Multiscale modeling at higher laser intensities corresponding to the fast ignition approach for Inertial Confinement Fusion : a relativistic treatment should be considered and collision operators with a large energy exchange are required.

One of the main challenges from the numerical point of view is to propose a general methodology to design macroscopic fluid models that take into account localized kinetic up-scaling effects (which represents the meso-scale). One approach will consist in considering fluid models, which are solved in the whole domain together with a localized kinetic upscaling that corrects the fluid model wherever it is necessary (non-equilibrium events occurring in the flow). This upscaling is obtained by solving a kinetic equation on the non-equilibrium part of the distribution function. This equation is solved only locally and is related to the fluid equation through a downscaling effect. We want to demonstrate that this approach applies to problems that have a hydrodynamic time scale as well as to problems with diffusion time scale.

The project will therefore combine physical modeling and mathematical analysis in order to achieve an understanding and propose a model of the plasma behavior over the various scales involved. The milestones involved in this project are therefore:

- set up a new phenomenology allowing to describe non-local effects in any geometry, and based on a state-of-the-art of mathematical modeling of hot plasmas;
- set up a multiscale model of the physical mechanisms at play at the different scales (micro, meso and macro scales), with a crucial emphasis on the connections between the scales ;
- propose a mathematical analysis and numerical development of the models, and provide systematic derivations of the connections between the scales.

This program therefore organizes naturally over the various scales at play in the problem and their connections: macroscale phenomenology ; kinetic at mesoscales ; statistical behavior at microscales.

LEMON Team

4. Application Domains

4.1. Coastal Oceanography

Participants: Arnaud Duran, 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

Participant: Vincent Guinot.

Floods have by 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 (5569up 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. Modeling of Multiperforated plates in turboreactors

In the turbo-engine, the temperature can reach 2000 K inside the combustion chamber. To protect its boundary, “fresh” air at 800 K is injected through thousands of perforations. The geometry of the network of perforations is chosen in order to optimize the cooling and the mechanical properties of the chamber. It has been experimentally observed that these perforations have a negative impact on the stability of the combustion. This is due to the interaction with an acoustic wave generated by the combustion. Due to the large number of holes (2000) and their small sizes (0.5 mm) with respect to the size of the combustion chamber (50 cm), it is not conceivable to rely on numerical computations (even with supercomputers) to predict the influence of these perforations.

In collaboration with ONERA, we develop new models which allow to take into account these multiperforated plates at the macroscopic scale.

4.3. Helioseismology

This collaboration with the Max Planck Institute for solar system, 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 5.2 . 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 recover sun spots.

MOISE Project-Team

4. Application Domains

4.1. Introduction

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), **air pollution** prediction systems, the prediction of **floods**, or the simulation of **mud flows** and **snow avalanches** for impact studies and regional planning.

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 MOISE 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.

4.2. Oceanography and the Ocean-Atmosphere System

Participants: Eric Blayo, Pierre-Antoine Bouttier, Vincent Chabot, Laurent Debreu, Jérémie Demange, Marc Honnorat, Christine Kazantsev, Eugène Kazantsev, François-Xavier Le Dimet, Florian Lemarié, Bénédicte Lemieux-Dudon, Maëlle Nodet, Antoine Rousseau, Arthur Vidard.

Keywords: Multi-resolution, Coupling Methods, Data Assimilation, Ocean, Atmosphere

Understanding and forecasting the ocean circulation is currently the subject of an intensive research effort by the international scientific community. This effort was primarily motivated by the crucial role of the ocean in determining the Earth's climate, particularly from the perspective of global change. In addition, important recent research programs are aimed at developing operational oceanography, i.e. near real-time forecasting of ocean circulation, with applications for ship routing, fisheries, weather forecasting, etc. Another related field is coastal oceanography, dealing for example with pollution, littoral planning, or the ecosystems management. Local and regional agencies are currently very interested in numerical modelling systems for coastal areas.

Both ocean-alone models and coupled ocean-atmosphere models are being developed to address these issues. In this context, the MOISE project-team conducts efforts mainly on the following topics:

- *Multi-resolution approaches and coupling methods*: Many applications in coastal and operational oceanography require high resolution local models. These models can either be forced at their boundaries by some known data, or be dynamically coupled with a large-scale coarser resolution model. Such model interactions require specific mathematical studies on open boundary conditions, refinement methods (like mesh refinement or stochastic downscaling), and coupling algorithms. The latter have also to be studied in the context of ocean-atmosphere coupled systems.

- *Advanced numerical schemes*: Most ocean models use simple finite difference schemes on structured grids. We are seeking for better schemes allowing both accuracy and good conservation properties, and dealing with irregular boundaries and bottom topography.
- *Data assimilation methods for ocean modelling systems*: The main difficulties encountered when assimilating data in ocean or atmosphere models are the huge dimension of the model state vector (typically 10^6-10^8), the strongly nonlinear character of the dynamics, and our poor knowledge of model error statistics. In this context, we are developing reduced order sequential and variational data assimilation methods addressing the aforementioned difficulties. We are also working on the assimilation of lagrangian data, of sequences of images, and on the design of data assimilation methods for multi-resolution models and for coupled systems.

Most of these studies are led in strong interaction with geophysicists, in particular from the Laboratoire des Ecoulements Géophysiques et Industriels (LEGI, Grenoble).

4.3. Glaciology

Participants: Eric Blayo, Maëlle Nodet.

Keywords: Inverse Methods, Data Assimilation, Glaciology, Ice Core Dating

The study of past climate is a means of understanding climatic mechanisms. Drillings in polar ice sheets provide a huge amount of information on paleoclimates: correlation between greenhouse gases and climate, fast climatic variability during the last ice age, etc. However, in order to improve the quantitative use of the data from this archive, numerous questions remain to be answered because of phenomena occurring during and after the deposition of snow. An important research aim is therefore to optimally model ice sheets in the vicinity of drilling sites in order to improve their interpretation: age scale for the ice and for the gas bubbles, mechanical thinning, initial surface temperature and accumulation when snow is deposited, spatial origin of ice from the drilling.

In another respect, ice streams represent an important feature of ice flows since they account for most of the ice leaving the ice sheet (in Antarctic, one estimates that ice streams evacuate more than 70% of the ice mass in less than 10% of the coast line). Furthermore, recent observations showed that some important ice streams are presently accelerating. Thus, we seek to improve models of ice sheets, by developing data assimilation approaches in order to calibrate them using available observations.

Another objective is the evaluation of the state of the polar ice caps in the past, and their interactions with the other components of the earth climate, in order to forecast their evolution in the forthcoming centuries. The joint use of models and data, through data assimilation techniques, to improve system description is relatively new for the glaciological community. Therefore inverse methods have to be developed or adapted for this particular purpose.

By gaining and loosing mass, glaciers and ice-sheets are playing a key role in the sea level evolution. This is obvious when regarding past as, for example, collapse of the large northern hemisphere ice-sheets after the Last Glacial Maximum has contributed to an increase of 120 m of sea level. This is particularly worrying when the future is considered. Indeed, recent observations clearly indicate that important changes in the velocity structure of both Antarctic and Greenland ice-sheets are occurring, suggesting that large and irreversible changes may have been initiated. This has been clearly emphasized in the last report published by the Intergovernmental Panel on Climate Change (IPCC). IPCC has further insisted on the poor current knowledge of the key processes at the root of the observed accelerations and finally concluded that reliable projections of sea-level rise are currently unavailable. In this context, our general aim is to develop data assimilation methods related to ice flow modelling purpose, in order to provide accurate and reliable estimation of the future contribution of ice-sheets to Sea Level Rise.

Development of ice flow adjoint models is by itself a scientific challenge. This new step forward is clearly motivated by the amount of data now available at both the local and the large scales.

4.4. River Hydraulics

Participants: Eric Blayo, Mehdi-Pierre Daou.

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 the level of accuracy which is required, 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. We tackled these issues, in the past in the framework of a partnership with the French electricity company EDF, and now thanks to another contract with ARTELIA Group.

POMDAPI Project-Team

3. Application Domains

3.1. Environmental sciences

Applications are in hydrogeology and water resources.

3.2. Energy sciences

Applications are in oil reservoir and sedimentary basin simulations, and in optimization of the power flow in an electricity transportation network.

SAGE Project-Team

4. Application Domains

4.1. Geophysics

The team has chosen a particular domain of application, which is geophysics. In this domain, many problems require solving large scale systems of equations, arising from the discretization of coupled models. Emphasis is put on hydrogeology, but the team also investigates geodesy, heat and mass transfer in soil, and granular materials. One of the objectives is to use high performance computing in order to tackle 3D large scale computational domains with complex physical models.

4.2. Hydrogeology

This is joint work with Geosciences Rennes at OSUR, Pprime at University of Poitiers and CDCSP at University of Lyon. It is also done in the context of the group Momas and previous Andra grants.

Many environmental studies rely on modelling geo-chemical and hydrodynamic processes. Some issues concern water resources, aquifer contamination, underground waste disposal, clean-up of former waste deposits, acid mine drainage remediation. Other issues, also related to energy, concern geothermy, unconventional gas, enhanced oil recovery, underground storage of CO2, underground storage of nuclear waste.

Simulation of contaminant transport in groundwater is a highly complex problem, governed by coupled linear or nonlinear PDAEs. Moreover, due to the lack of experimental data, stochastic models are used for dealing with heterogeneity. The main objective of the team is to design and to implement efficient and robust numerical models, including Uncertainty Quantification methods.

Recent research showed that rock solid masses are in general fractured and that fluids can percolate through networks of inter-connected fractures. Fractured media are by nature very heterogeneous and multi-scale, so that homogenisation approaches are not relevant. The team develops a numerical model for fluid flow and contaminant transport in three-dimensional porous fractured media.

An important output is the parallel scientific platform H2OLab, running on clusters, grids and machines available in supercomputing centers.

STEEP 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 has already initiated 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).

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 is involved in the ESNET project, bearing on the characterization of local Ecosystem Services NETworks; the project is 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 may be useful for the LUCC community at large, independently of the ESNET project needs.

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 retraces the historic path of these theories and models. They

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[0] Congestion, cost and time spent for the transport, etc.

[0] Changes in modality choice

[0] CO2 emissions, air pollution, noise nuisance, etc.

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 projects CITiES ("*ANR Modèles Numériques*") and TRACER (Ecos Nord Venezuela). 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.

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[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 (see Figure 2). 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 50'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*.

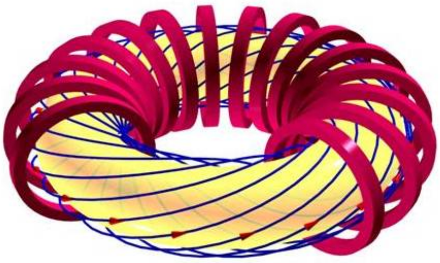

Figure 2. Poloidal coils and magnetic field lines geometry inside a tokamak

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. We plan to supervise a new PhD with CEREMA (Centre d'études et d'expertise sur les risques, l'environnement, la mobilité et l'aménagement) in Strasbourg. 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) [81].

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 work concentrates on the protection of cultures of photosynthetic organisms against their pests or their competitors. The forms of cultures that 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 invading species which can be harmful to the cultures; we opt for protecting the culture through the use of biocontrol agents which are, generically, natural enemies of these noxious populations [6].

In crop production, biological control is indeed a very promising alternative to pesticide usage; the use of predators, parasitoids or pathogens of crop pests in order to fight them has many advantages with respect to environmental protection, health of the consumers and the producers, the limited development of resistance (compared to chemicals),... It 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. 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.

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 [105] 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 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. 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.

4.6. Software development

4.6.1. ODIN

We are developing ODIN, a software platform for the supervision of bioreactors. ODIN [80] supports the smart management of bioreactors (data acquisition, fault diagnosis, automatic control algorithm,...). This C++ application (working under Windows and Linux) is structured in order to rapidly develop and deploy advanced control algorithms through the use of a Scilab interpreter. It also contains a Scilab-based process simulator (developed jointly with Inria Chile) which can be harnessed for experimentation and training purposes. ODIN is made of different modules which can be distributed along different platforms, and which interact through CORBA.

It has been implemented and validated with four different applications in four different laboratories. A licence with the start-up BioEnTech was signed for remote monitoring of anaerobic digesters.

4.6.2. In@lgae

The simulation platform In@lgae is jointly developed with the Inria Ange team. Its objective is to simulate the productivity of a microalgae production system, taking into account both the process type and its location and time of the year. A first module (Freshkiss) developed by Ange computes the hydrodynamics, and reconstructs the Lagrangian trajectories perceived by the cells. Coupled with the Han model, it results in the computation of an overall photosynthesis yield. A second module is coupled with a GIS (geographic information system) to take into account the meteorology of the considered area (any location on earth). The evolution of the temperature in the culture medium together with the solar flux is then computed. Finally, the productivity in terms of biomass, lipids, pigments together with CO_2, nutrients, water consumption, ... are assessed. The productivity map which is produced can then be coupled with a resource map describing the availability in CO_2 nutrients and land.

CARMEN Team

4. Application Domains

4.1. Scientific context: the LIRYC

Our fields of application are naturally: electrophysiology and cardiac physiopathology at the tissue scale on one side; medical and clinical cardiology on the other side.

The team's research project is part of the IHU LIRYC project, initiated by Pr. M. Haissaguerre. It is concerned by the major issues of modern electrocardiology: atrial arrhythmias, sudden death due to ventricular fibrillation and heart failure related to ventricular dyssynchrony.

We aim at bringing applied mathematics and scientific computing closer to biomedical research applied to cardiac rhythmology and clinical cardiology. It aims at enhancing our fundamental knowledge of the normal and abnormal cardiac electrical activity, 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 the 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:

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 vein.

At the ventricula level, we focus on (1) modeling the complex coupling between the Purkinje network and the ventricles and (2) modeling the structural heterogeneities at the cellular scale, taking into account the complex organisation and disorganisation 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.

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 intracellular 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 [42] 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.

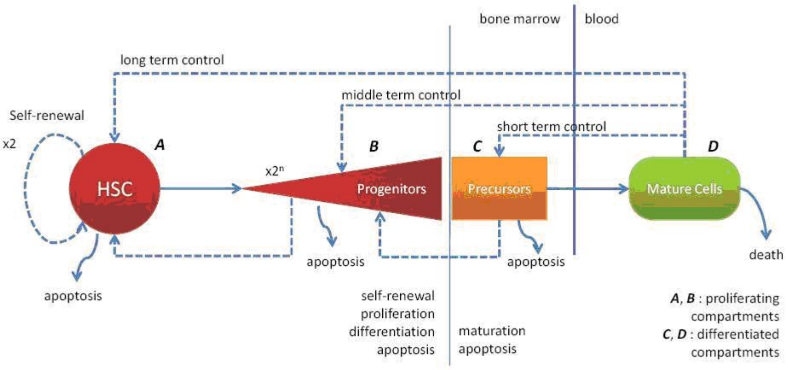

Figure 3. Scheme of Erythropoiesis Modelling ([33]). Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) 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 [46]. 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 ([41], [38]), chronic myelogenous leukemia [43]).

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.

(iii) Coagulation: platelet lineage

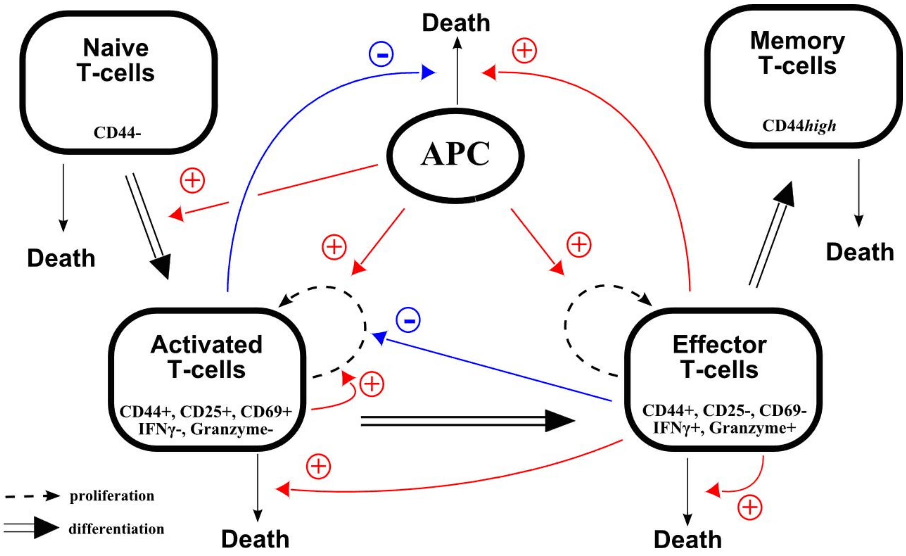

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naive T-cells. These latter, once activated, differentiate into activated cells 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.

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. [36]) 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 [44]. 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 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 [9]. 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 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 of populations structured according to relevant phenotypes – in collaboration with our biologist partners within the Institut Universitaire de Cancérologie (IUC) of UPMC, we tackle the problem of understanding and limiting a) evolution from pre-malignancy to malignancy in cell populations, and b) in established cancer cell populations, evolution towards (drug-induced) drug resistance. Environmental pressure guiding evolution is of various natures, 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 [59], [58] [40] are akin to models used in ecology for adaptive dynamics.

Multi-scale modelling of EMT. The major step from a benign tumour that can be eradicated by surgery and an invasive cancer is the development step at which cells detach from the tumour mass and invade individually the surrounding tissue [0]. The invasion is preceded by a transition (called EMT - epithelial mesenchymal transition) of the cancer phenotype from an epithelial type to a mesenchymal type cell. We so far worked on multi-scale modelling of EMT [0], and the step by which invading cancer cells enter blood vessels, called intravasation [0]. We now perform in-vitro simulations of cancer cell invasion for Non Small Cell Lung Cancer (NSCLC) having a 5-year survival fraction of about 20%, and for breast cancer. Under development (in collaboration with our biologist partners within the IUC for the experimental part) is also a phenotype-structured PDE model of the interactions between colonies of MCF7 breast cancer and adipocyte stromal support populations.

4.2. Cancer therapies and their optimisation

Drugs. 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 (i.e., this is not L^2 nor L^1, but L^∞ optimisation) in healthy cell populations and avoiding the emergence of resistant cell clones in cancer cell populations [49], [58] [4], [40]. Prior to using optimisation methods, we design models of the targeted cell populations (healthy and tumour, including molecular or functional drug targets [48]) by PDEs or agent-based models [3], and molecular pharmacological (pharmacokinetic-pharmacodynamic, PK-PD) models of the fate and effects of the drugs used, usually by ODE models. A particular aspect of such modelling is the representation of multi-cellular spatio-temporal patterns emerging from therapies.

Radiotherapy. Radiation is still a major treatment in cancer. We have recently published new results on this topic, pleae refer to the *New Results* section.

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4.3. 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 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.

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 include 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 [63].

One other 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, wound healing in vivo and morphogenetic movements involving closure of holes in epithelia have been the object of many studies (including some involving members of this project like [47]). Several theoretical models have also been proposed recently for the advancement of tissue covering unoccupied areas (see, for instance, [46]). It is particularly interesting to study epithelial gap closure in vivo. However, the complexity of the process and the difficulty to measure relevant quantities directly and to control the parameters in vivo, lead people to seek alternative systems where epithelial gap closure can be studied under better-defined and better-controlled conditions.

4.4. Contraction of acto-myosin structures in morphogenesis and tissue repair

In 2014, L. Almeida, I. Cheddadi, C. Emako-Kazianou, P. Bagnerini [0], A. Jacinto [0], P. Patricio [0], B. Ladoux [0] and N. Gov [0] have continued to investigate the dependence of physical and biological mechanisms of actomyosin cable formation and wound closure depending on the geometry of the wound and adhesion to the substrate, with particular emphasis on the effect of the wound edge curvature. We extended our work from in vivo studies to in vitro situations taking advantage of a collaboration with the group of Benoît Ladoux who did experiments on cell monolayers of human keratinocytes and of MDCK cells. We could single out some similar geometry dependence of the wound closure strategies between these two settings indicating the existence of conserved mechanisms that should be very general across living beings.

In our model under development, we consider viscous behaviour and friction in the tissue plus boundary terms associated to cable and lamellipodial forces. The numerical simulations obtained using this model are in good agreement with the experimental results. This work is attracting considerable attention from the community.

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4.5. Protein polymerisation

Protein polymerisation is the key feature of amyloid diseases, among which we can quote Alzheimer's, Prion (in particular variant Creutzfeldt-Jakob disease, epidemically linked to bovine spongiform encephalopathy, or so-called "mad cow", disease), Parkinson's, Huntington's diseases. 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 [51], [50]. Hence the European starting grant SKIPPER^{AD}, which follows the ANR project TOPPAZ, came up very naturally from the encounter with Human Rezaei, a biologist expert in amyloid diseases at INRA Jouy-en-Josas. Moreover, this field of applications brings new questions to us, which is both a stimulation for our mathematical research and a very promising tool for the biologists.

4.6. 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 permit to account for many of the observed phenomena (e.g. [0], [0]). They furthermore permit calculation of the stress tensor in the tissue. ABMs resolving cells at higher resolution [0] permit to calculate cell deformation as a response 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. This permits relating stress and strain in tissues and the deformation and stress a cell feels at subcellular scale. We extended a deformable cell model towards cell-division which enables us to calculate precise stress - strain relationships for cells, that later can be used to calibrate forces in center-based models. This is fundamental to understand the impact of mechanical stress on cell cycle progression or other cell decisions. Moreover, we established a model to explain the proliferation pattern of cells growing in closed capsules.

4.7. Liver modelling

Liver is the main detoxifying organ of the human body and can regenerate up to about 70% of its mass. It pursues its task due to a complex tissue architecture, with hepatocytes aligning along micro-capillaries and forming a dense network. Incidence rate of liver diseases are steadily increasing, liver cancer ranks 6th among all cancers. About one person in 12 suffer from viral hepatitis, which makes 500 million people worldwide. Hepatitis B and C as well as misuse of drugs or alcohol are major reasons to develop 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 being developed approaches addressing the tissue scale ([57], [0], [0], [0], [0]). We are developing 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 pharmacokinetics in liver and liver cancer, and model-based prediction of in-vivo drug toxicity from in-vitro measurements [0]. The research work is performed within the EU project NOTOX, the BMBF project VIRTUAL LIVER NETWORK and the ANR project IFLOW.

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MASAIE Project-Team

4. Application Domains

4.1. Metapopulation models

Heterogeneity plays an important role in many infectious disease processes. For instance, spatial heterogeneity is a strong determinant of host-parasite relationships. In modeling spatial or geographic effects on the spread of a disease, a distinction is usually made between diffusion and dispersal models. In diffusion models, spread is to immediately adjacent zones, hence the phenomenon of traveling waves can appear. These models traditionally use partial differential equations. However, there are some important situations that cannot be modeled by PDE. This is the case when the space considered is discrete. For example, when we have to consider sparsely populated regions, the human population is located in patches. The organization of human-hosts into well-defined social units such as families, villages or cities, are good examples of patches. Another example arises in the study of the human African Trypanosomiasis. The vector is the tse-tse fly, and it is known that flies take fewer blood meals in villages than in coffee plantations where the villagers work during the day. For such situations where human or vectors can travel a long distance in a short period of time, dispersal models are more appropriate. These models consider migration of individuals between patches. The infection does not take place during the migration process. The situation is that of a directed graph, where the vertices represent the patches and the arcs represent the links between patches. During the last decade, there has been increased interest in these deterministic metapopulation disease models. We have generalized to n patches the Ross-Macdonald model which describes the dynamics of malaria. We incorporate in our model the fact that some patches can be vector free. We assume that the hosts can migrate between patches, but not the vectors. The susceptible and infectious individuals have the same dispersal rate. We compute the basic reproduction ratio $\mathcal{R}_0$. We prove that if $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable. When $\mathcal{R}_0 > 1$, we prove that there exists a unique endemic equilibrium, which is globally asymptotically stable on the biological domain minus the disease-free equilibrium.

MASAIE is developing, in the framework of the CAPES-COFECUB project (see international program), a metapopulation model for dengue. This model is for the state of Rio and is using the data of foundation FIOCRUZ.

MODEMIC Project-Team

4. Application Domains

4.1. Wastewater treatment systems

The water resources of our planet are limited, and today the quality of drinking water is considered to be responsible of more human deaths than malnutrition. Pollution and over-exploitation of water resources affect almost all the water reservoirs on Earth. Preserving the quality of water has thus become a worldwide problem. The industry of decontamination is thus a necessity, but waste-water treatment is costly and requires large plants. It relies on the use of micro-organisms that concentrate toxic soluble substances into sludge (that can be used as a fertilizer in agriculture). Today, a water decontamination plant costs about 1000 to 5000 euros per inhabitant. 30 to 40% of its running costs are devoted to the energy necessary for pool ventilation.

The waste-water treatment industry use software to optimize the plant design (number, size, interconnections of tanks), but design and improvements of bio-processes remain costly. This is why modelling allows numerical simulations of *virtual* bio-processes that can save substantial amount of money, avoiding tests at a real scale.

There is presently a growing need to conceive treatment systems in a more global framework, including the valorization of the “outputs” such as:

- the biogas production,
- the reuse of treated water for agriculture or dam refill in case of drought.

This requires to re-think the use of the models or to couple them with other models with new outputs and novel criteria to be optimized.

This is our most important domain of transfer and dissemination.

4.2. Environmental microbiology

Chemostat-like models (see Section 3.1.1) are also quite popular in theoretical marine ecology or in soil bio-chemistry, because micro-organisms play again a crucial role in the bio-geo-chemical cycles on Earth. Questioning are here a bit different than the ones depicted in Section 4.1 , because it is much more oriented towards comprehension and prediction than decision making (at the present time). Grasping the role of the microbial biodiversity appears to be an everlasting and common important question among scientists of various domains.

Nevertheless, mathematical models are quite similar but with some specificity (much more resources are available in marine microbiology; the spatial heterogeneity play a crucial role in underground processes).

A recent trend of considering natural microbial ecosystems on Earth to be able to delivering new ’eco-systemic services’ has emerged, especially in terms of bio-remediation. Modelling and simulating tools are much relevant as in site experiments are quite costly and time-consuming.

4.3. Bioprocesses industry

Several industries use micro-organisms or yeasts to product substances of commercial interest (in pharmaceutics, green biotechnology, food making...). Novel investigation techniques in microbiology (such as multistage continuous bioreactors) brings new insights on the metabolic functioning of the various strains. This conducts to revisit old models such as Monod’s one, and to look for new estimation and piloting strategies. Those questions are quite closed from the ones studied in 4.1 and 4.2 , although the ecological dimension is less present (most of the culture are pure ones). The team is naturally solicited to contribute together with the specialists about problems related to modelling, simulation and control of these bio-processes.

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.

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 closed 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 [5], [6], analysis of neurosecretory patterns [13] and modeling of GPCR (G-Protein Coupled Receptors) signaling networks [8]. 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 [42].

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.* [62], [66], [65] and the references therein), nevertheless there are only very few studies showing realistic electrocardiograms obtained from partial differential equations models. Our goal is to find a compromise between two opposite requirements: on the one hand, we want to use predictive models, and therefore models based on physiology, on the other hand, we want to use models simple enough to be parametrized (in view of patient-specific simulations). One of the goal is to use our ECG simulator to address the inverse problem of electrocardiology. In collaboration with the Macs/M3disym project-team, we are interested in the electromechanical coupling in the myocardium. We are also interested in various clinical and industrial issues related to cardiac electrophysiology, in particular the simulation of experimental measurement of the field potential of cardiac stem cells in multi-electrode arrays.

SISYPHE Project-Team

3. Application Domains

3.1. Medical applications of modeling, signal analysis and control

- *3D cardiac modeling for personalized medicine.* Our main contribution to Inria's collective efforts in this field (project-teams Asclepios, MACS, REO, Sisyphe) is the so-called "Bestel-Clément-Sorine" model of contraction of cardiac muscle [39], at the origin of the 3D electromechanical direct and inverse modeling of the heart at Inria. This model is based on ideas originating from the kinetic equation theory, used to model, on the molecular scale, the controlled collective behavior of actin-myosin nanomotors at the root of muscle contraction. The classical Huxley model was recovered on the sarcomere scale by using moment equations and a controlled constitutive law on the tissue scale was obtained using the same type of scaling techniques. The model, now embedded in heart simulators, is used in various studies [51], [3], [54], [53].

- *Semiclassical analysis of cardiovascular signals.* This work began with the article [41] and the PhD of M. Laleg-Kirati [47], [46], [49]. The theory and a validation of a new method of blood pressure analysis are now published [17], [48].
The main idea is to consider a signal $x \to y(x)$ to analyze as the multiplication operator $\phi \to y\phi$ on some function space, and to analyze it as a potential. The signal is represented by the spectrum of an associated Schrödinger operator, combined with a semi-classical quantification: $-h^2\frac{d^2}{dx^2} - y(x)$ with $h > 0$ small. For signals looking as "superpositions of bumps" (e.g. the systolic pulse, the dichrotic notch for the arterial pulse pressure), this leads to some kind of nonlinear Fourier analysis [17]. The spectral parameters associated with the arterial pressure can be useful cardiovascular indices, e.g. for noninvasive blood flow estimation [48]. In the arterial pressure case, this is equivalent to approximate the traveling pressure pulse by a N-soliton solution of a Korteweg-de Vries (KdV) equation [41] and using ideas similar to the Lax pair representation of N-solitons and proof technique for the weak dispersion limit of KdV. A striking result is that an N-soliton is a very good representation of the arterial pressure waveform for values of N as small as $N = 3$. The representation of pulse-shaped signals is parsimonious, having only $2N$ parameters [55].

- *Multiscale signal analysis of cardiovascular signals:* collaboration with Julien Barral (former member of Sisyphe) and partners of the ANR project DMASC. The starting point was the common idea that "A Healthy Heart Is a Fractal Heart". We have developed a method to test the existence of scale laws in signals and applied it to RR signals: the heart rate is not always fractal or even multifractal in an Healthy Heart [19].

- *Modeling and control of CARMAT Total Artificial Heart.* This TAH has been implanted for the first time in a patient in Dec 2013. We have contributed to this industrial project since 2008 on modeling and control questions during the post-doc of Karima Djabella (now engineer at CARMAT), Frédéric Vallais and the two-year contract for supervising Julien Bernard (CARMAT control engineer). It was an opportunity to exploit some results on the baroreflex control [42] or heart rate variability during exercise [40].

- *Glycemic control in Intensive Care Units (ICUs):* Blood glucose is a key biological parameter in ICU since the study of van den Berghe et al [60] who demonstrated decreased mortality in surgical intensive care patients in association with tight glycemic control (TGC), based on intensive insulin therapy. In their work, however, there was only one ICU and the protocol was not formalized. Trying to decrease mortality in standard ICUs by using computer aided glycemic control is still a challenge. Previous studies have failed because of high rates of severe hypoglycemia. The last one was NICE-SUGAR [57] with a 2% increase in mortality (death ratio from any cause within 90 days after randomization compared between control and TGC patients). In cooperation with Pierre Kalfon (Intensive Care, Hospital of Chartres) and in the framework of a CIFRE contract with a small medtech company LK2 (Tours, France), we have studied the origins of these failures and proposed more robust control algorithms tuned using a database of representative "virtual patients". See [44] and the PhD of A. Guerrini, [43]. A first version of the controller has been tested in a large clinical study CGAO-REA [14].

3.2. Engineering applications of modeling, signal analysis and control

Identification of nonlinear systems: from algorithms to a popular matlab toolbox:
Block-oriented nonlinear system identification with Jiandong Wang (Associate Professor, Beijing University, China) [58]; Development of the Matlab System Identification ToolBox (SITB).

Identification of transmission line characteristics: from algorithms to electronic experiments. Collaboration with CEA LIST (Lab of applied research on software-intensive technologies) and LGEP (Laboratoire de génie électrique de Paris) with Florent Loete [50] (ANR projects SEEDS, 0-DEFECT, INSCAN, SODDA).
We have extended to some networks the seminal work of Jaulent [45] for the real line: all the information contained in a measured reflection coefficient can be obtained by solving an inverse scattering problem for a system of Schrödinger or Zakharov-Shabat equations on the graph of the network, which allows one to recover the geometry of the network and some electrical characteristics for nonuniform lossless electrical star-shaped networks [26]. An efficient method to solve the associated Guelfand-Levitan-Marchenko equations has been studied and is used in the software ISTL that has been developed in Sisyphe [59], [56]. This development will continue in the project-team I4S. An engineering methodology based on this approach has been described [29] and some first experimental results obtained [36], [50].

Monitoring and control of automotive depollution systems: with RENAULT (Karim Bencherif, Damiano Di Penta and PhD students): [52], [20], [38].

3.3. Modeling and optimizing patient pathways in hospital

This research theme was inspired by the observation that the practice of modern industrialized medical care proceeds by queueing and forwarding patients from one step of care to the next, with each step involving specialized personnel and machinery. Whereas the human competence and machine performance available in hospital are both highly evolved, the deployment of these resources for the patient's benefit is problematic.

If we change our point of view and, rather than look in the traditional way at the hospital as a collection of "vertical" silos (emergency room, cardiac ward, respiratory ward, operating rooms, imagery services, blood services, logistics, etc.), we instead consider the patient's "horizontal" trajectory crossing through many different silos, we can see significant problems. In between each step, whose value added part typically lasts at most a few minutes, there are long stretches of time (on the order of hours) during which the patient simply waits for the hospital to arrange the next step of care — with serious consequences:
- delayed treatment is directly correlated with increased rates of hospital acquired nosocomial infection for the immuno-compromised and to loss of autonomy for the elderly;
- the cost in terms of scarce resources (for example, bed-hours in hospital) is significant, but the root causes of these costs due to problems at the interfaces between silos are hard to observe since they do not fit neatly into the hospital's traditional hierarchy;
- the slow and error prone hand-offs of information between silos are dangerous for the patient who is vulnerable to medical errors. In the US, for example, it is estimated that there are 100,000 deaths per year attributable to hospital error (triple the number due to road traffic accidents by way of comparison).