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MATHEMATICAL MODELS IN HEALTH SCIENCES

NANTES
20>22 JUNE
2018

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TOMÁS ALARCÓN
ICREA, CENTRE DE RECERCA MATEMÀTICA, BARCELONA

THIERRY COLIN
UNIVERSITÉ DE BORDEAUX

CÉDRIC GALUSINSKI
UNIVERSITÉ DE TOULON

JACQUES LE PENDU
INSERM, UNIVERSITÉ DE NANTES

KENT-ANDRE MARDAL
UNIVERSITY OF OSLO

ROBERTO NATALINI*
CONSIGLIO NAZIONALE DELLE RICERCHE, ROMA

LUIGI PREZIOSI
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RICARDO RUIZ-BAIER
UNIVERSITY OF OXFORD

CHRISTIAN SCHMEISER
UNIVERSITY OF VIENNA

THOMAS STIEHL
UNIVERSITÄT HEIDELBERG

NICOLAS VAUCHELET
UNIVERSITÉ PARIS 13

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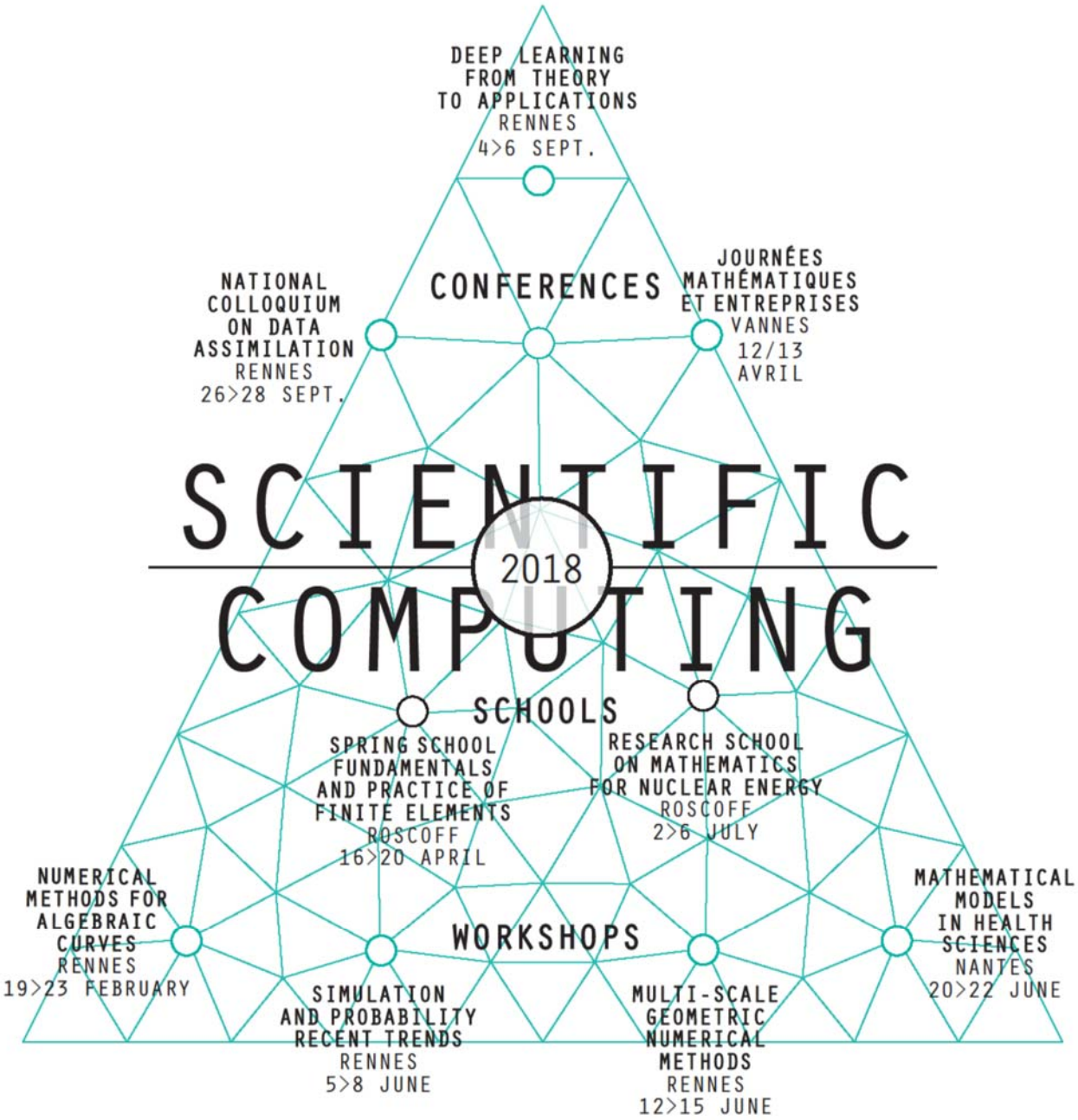

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Coming to the Campus

From downtown: At the station "Commerce" take the tramway line 2 in the direction of "Orvault-Grand Val". Get off at the station "Michelet Sciences". The cost of a one-hour-valid ticket is 1,60 Euros and there are some vending machines at each stop. You can also buy a book of 10 tickets which costs 14,70 Euros.

From the train station: Upon your arrival at the main station (La Gare), take the North exit (Sortie nord) and walk in the direction of the tramway stop "La Gare" which is in front of the main entrance of the station. Take the tramway line 1 in the direction of "François Mitterrand", get off at "Commerce" then take the tramway line 2 in the direction of "Orvault-Grand Val" and get off at "Michelet Sciences".

Attention: The vending machines may not take non-France issued credit/Banking cards. Almost certainly, they will not take US issued credit/ATM cards.
For detailed bus and tramway schedules please visit **TAN** (http://www.tan.fr).

From the Nantes-Atlantique airport (http://www.nantes.aeroport.fr):

By bus: You can get to the city center by the airport shuttle bus (TAN AIR Shuttle) in 20 minutes. The final stop of the shuttle is "Commerce" and there is one bus every 30 minutes. From there you can take the tramway line 2 in the direction of "Orvault Grand Val" and get off at "Michelet Sciences". The cost of a one-hour-valid ticket is 9,00 Euros, valid for tramway and shuttle bus.

By taxi: At the main entrance of the Hall 4 you will find a taxi shelter where you can call for a taxi to pick you up. The cost is around 40 Euros.

Once on the campus: Walk to **building 2 (Amphi Pasteur)** where the conference will take place (see map 2).

Accommodation

The speakers of the conference will be accomodated in the hotel : (see hotels maps)

« Hôtel Amiral »
26 bis Rue Scribe
44000 Nantes
Phone +33 (0)2 40 69 20 21

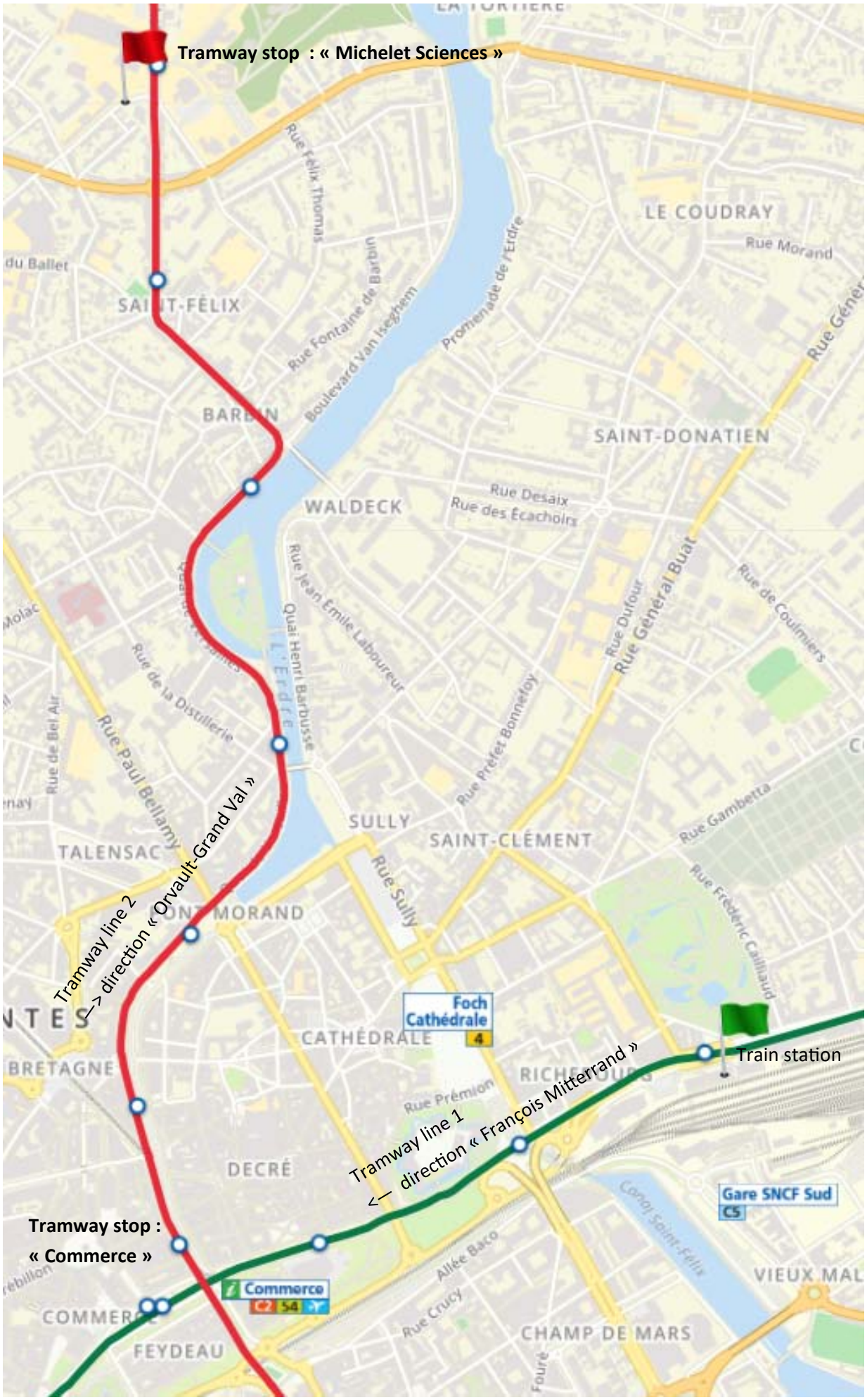
The participants will be accomodated in the hotel :

«Duc de Bretagne »
2/4 Rue Emile Péhant
44000 Nantes
Phone +33 (0)2 40 35 25 02

Lunch will be taken at the Restaurant Universitaire « La Lombarderie» (see map 2).

The gala dinner will take place at the restaurant « le 1» (see map 3).

Map 1 : Train station - Campus Sciences



Map 2: Campus Sciences - Amphi Pasteur (Building 2)

Hotels maps

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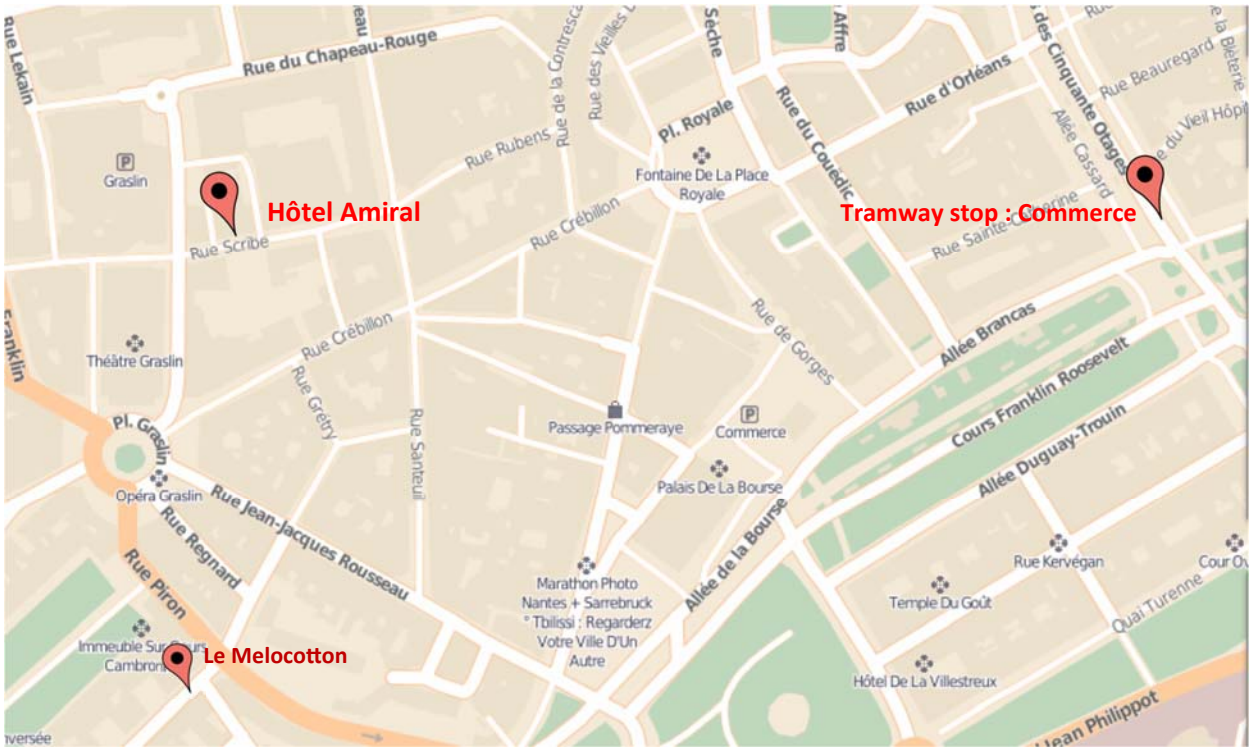

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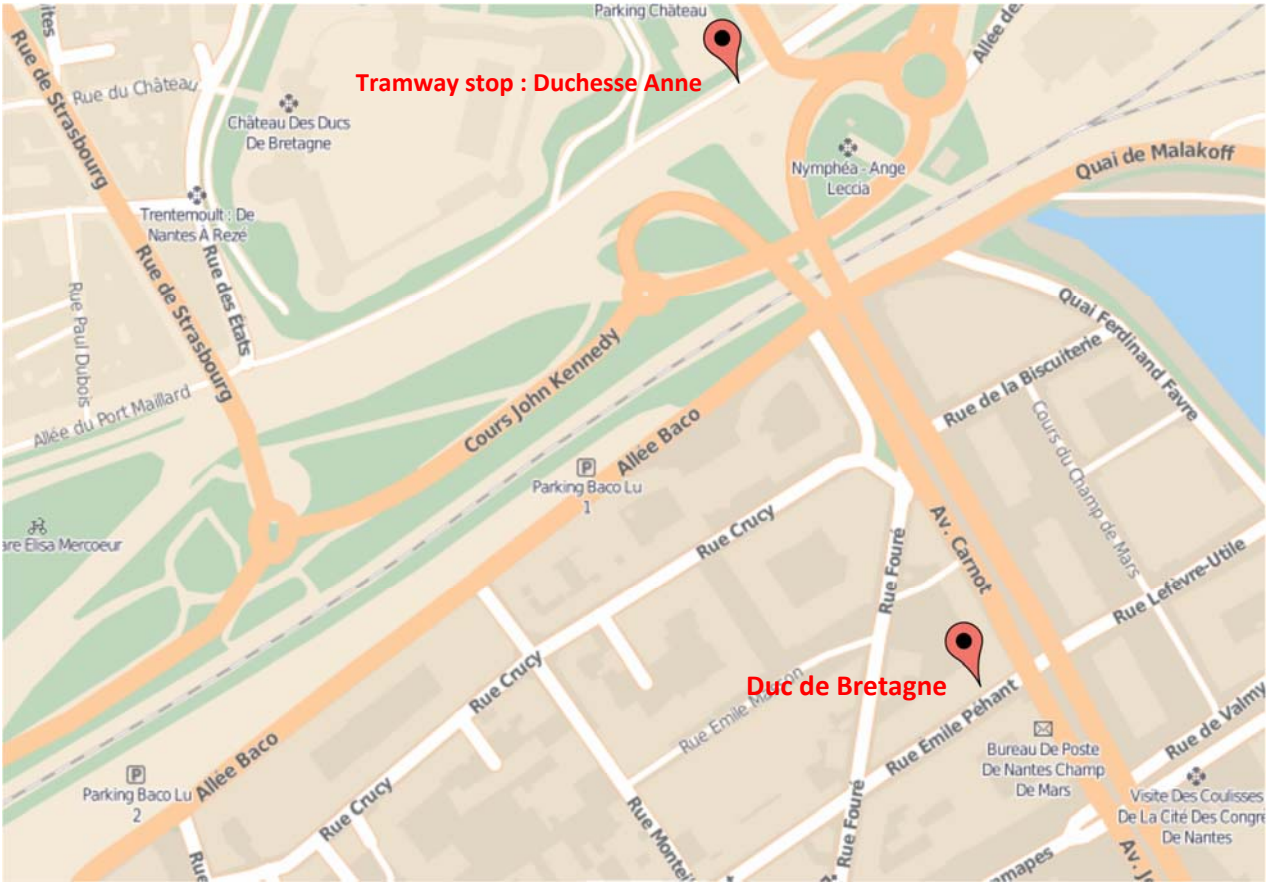

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Enter the login and the password that you will find on the backside of your badge.
Mark with a cross the box "*J'ai pris connaissance de la charte d'utilisation et j'en accepte les termes*."
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To have access to the room, please see the secretaries.

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The library - Centre Régional de Documentation Mathématique (CRDM)

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List of participants

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Bader	Fakhrielddine	Université de Nantes
Berthon	Christophe	Université de Nantes
Bessemoulin	Marianne	CNRS - Université de Nantes
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Stiehl	Thomas	Heidelberg University - Germany
Twarogowska	Monika	ENS de Lyon
Vauchelet	Nicolas	Université Paris 13

Program

Campus Science, Building 2 Amphi Pasteur

Wednesday June 20th	
09h-10h	Welcome
10h-10h10	Opening
10h10-11h00	Cédric Galusinski
11h00-11h20	Coffee break
11h20-12h10	Kent-Andre Mardal
12h20-14h00	Lunch
14h00-14h50	Ricardo Ruiz Baier
14h50-15h20	Monika Twarogowska
15h20-15h50	Emmanuel Bakare
15h50-16h20	Coffee beak
16h20-17h10	Christian Schmeiser
17h10-17h40	Vuk Millisic
20h00	**Gala dinner**

Tuesday June 21st	
9h30-10h20	Tomás Alarcón
10h20-10h50	Fatima Mroué
10h50-11h10	Coffee break
11h10-12h00	Jacques Le Pendu
12h00-14h00	Lunch
14h00 -14h50	Luigi Preziosi
14h50-15h40	Vuk Millisic
15h40-16h10	Coffee break
16h10-16h40	Jonathan Stéphano
17h00-18h00	Colloquium : Julie Delon (salle des séminaires)

Friday June 22th	
9h30-10h20	Thomas Stiehl
10h20-10h00	Coffee break
11h100-12h00	Nicolas Vauchelet
12h00	Lunch

Conferences

Tomás Alarcón (ICREA, Centre de Recerca Matemàtica, Barcelona)

Unlocking the pluripotent phenotype: A multiscale model of the epigenetic regulation of cell fate and plasticity.

Understanding the control of epigenetic regulation is key to explain and modify the aging process. Because histone-modifying enzymes are sensitive to shifts in availability of cofactors (e.g. metabolites), cellular epigenetic states may be tied to changing conditions associated with cofactor variability. The aim of this study is to analyse the relationships between cofactor fluctuations, epigenetic landscapes, and cell state transitions. Using Approximate Bayesian Computation, we generate an ensemble of epigenetic regulation (ER) systems whose heterogeneity reflects variability in cofactor pools used by histone modifiers. The heterogeneity of epigenetic metabolites, which operates as regulator of the kinetic parameters promoting/preventing histone modifications, stochastically drives phenotypic variability. The ensemble of ER configurations reveals the occurrence of distinct epi-states within the ensemble. Whereas resilient states maintain large epigenetic barriers refractory to reprogramming cellular identity, plastic states lower these barriers, and increase the sensitivity to reprogramming. Moreover, fine-tuning of cofactor levels redirects plastic epigenetic states to re-enter epigenetic resilience, and vice versa. Our ensemble model agrees with a model of metabolism-responsive loss of epigenetic resilience as a cellular aging mechanism. Our findings support the notion that cellular aging, and its reversal, might result from stochastic translation of metabolic inputs into resilient/plastic cell states via ER systems.

Cédric Galusinski (Université de Toulon)

3D Vessel reconstruction from partial or full C-T scan data.

In collaboration with A. Al Moussawi and C. Nguyen.

The goal of this talk is first to to introduce the 3D reconstruction of blood vessels from a limited number of 2D transversal cuts obtained from scanners (C-T scans). This is motivated by the fact that data can be missing. The difficulty of this work is to connect the blood vessels between some widely spaced cuts. We identify the vessels on each transversal cut as a mass to be transported along a graph which allows to determine the bifurcation points of vessels. Specifically, we are interested in branching transportation to model an optimized graph associated to the network of vessels. Adapted cost functions are then selected. We are then able to reconstruct the 3D vessels identified as the zero level of a 3D level set function whose 2D transversal cuts fit to data (where they are known).In a second part, when the whole scanners data are available,a global reconstruction is proposed with reconstruction improvements in order to overcome low resolution of C-T scan at the vessel scale and to overcome patient motion during the scan. Vessel deformations are also presented.

Jacques Le Pendu (CRCINA, Inserm, Université d'Angers, Université de Nantes)

Norovirus infection and vaccine development.

Noroviruses represent the major single cause of gastroenteritis worldwide. They are responsible for a disease that is generally self-limited but can be severe and life-threatening in the elderly, in immunocompromized patients and in young children of developing countries. They are small non-enveloped viruses that can evolve rapidly and are equipped with a single capsid protein that may be subject to epochal evolution of epidemiologically dominant strains, similar to Influenza virus. To infect cells, the capsid protein attaches to carbohydrates exposed at the surface of cells lining the small intestine. The relative affinity of virus strains that undergo epochal evolution has been associated with their epidemiological impact, suggesting that immune-escape variants may become more pathogenic. Vaccine development is in progress. However, the results from the first trials in volunteers indicate that the extant vaccines are imperfect, only decreasing the severity of symptoms, but not the infection rate. The evolution of the virus under immune pressure in natural conditions and in vaccine conditions therefore should be evaluated in order to determine under which conditions an imperfect vaccine may lead to increased pathogenicity of the virus in the non-immunized. To this aim a modelling effort is ongoing in collaboration with researchers from the Jean Leray laboratory in Nantes.

Kent-Andre Mardal (University of Oslo)

Mathematical modeling of the glymphatic system.

The newly proposed glymphatic system offers a potential explanation for how the brain (which mostly lack a lymphatic system) clears waste. As malfunctioning waste clearance seems to be a main problem in diseases such as Alzheimer, where accumulation of amyloid-beta plaques is one of the hallmark features, an understanding of this process may have huge potential. The glymphatic system remains controversial. It is a biomechanical theory that links the transport between the cerebrospinal fluid, the peri- and paravascular spaces that surrounds the blood vessels and the extracellular matrix and has as such been the subject of subject of many recent modeling efforts.
In this talk we present an overview of mathematical models for the glymphatic system and include our own results in this type of modeling.

Luigi Preziosi (Politecnico di Torino)

Multi-level mathematical models for cell migration in dense fibrous environments.

Cell-extracellular matrix interaction and the mechanical properties of cell nucleus have been demonstrated to play a fundamental role in cell movement across fibre networks and micro-channels and then in the spread of cancer metastases.

The lectures will be aimed at presenting several mathematical models dealing with such a problem, starting from modelling cell adhesion mechanics to the inclusion of influence of nucleus stiffness in the motion of cells, through continuum mechanics, kinetic models and individual cell-based models.

Ricardo Ruiz Baier (University of Oxford)

Mixed formulations for coupled diffusion-stress systems and some applications in biomechanics.

In this talk we will present an overview of a family of mixed-primal and mixed-mixed partial differential equations governing the interaction between the deformation of elastic and hyperelastic bodies and nonlinear reaction-diffusion mechanisms. We will address unique solvability of the coupled problems in the context of fixed-point operators, and will discuss the construction of suitable mixed finite element schemes for their numerical approximation. This general formalism will be then used to solve specific applicative problems, related for instance, to the modelling of cardiac electromechanics. Our approach in turn suggests a natural way of incorporating so-called mechano-electric feedback effects.

Christian Schmeiser (University of Vienna)

Simulation of cell-cell interaction by the Filament Based Lamellipodium Model (FBLM).

The FBLM, a two-dimensional anisotropic two-phase continuum model for the dynamics of the actin network in the lamellipodium, can be used to describe cell-cell interaction in monolayers spread on flat substrates. First attempts in this direction will be presented, taking into account steric repulsion as well as cell-cell adhesion. (joint work with A. Brunk, D. Peurichard, and N. Sfakianakis).

Thomas Stiehl (Universität Heidelberg)

Understanding clonal dynamics in blood cancer - insights from mathematical modeling.

Acute leukemias are cancerous diseases of the blood forming (hematopoietic) system. The leukemic cell bulk is derived from a small and heterogeneous population of leukemic stem cells. Upon expansion, the leukemic cells out-compete healthy blood production which results in severe clinical symptoms.

To study the interaction of leukemic and healthy cells, we propose mathematical models of hierarchical cell populations. Cell competition and selection are mediated by various biologically inspired feedback mechanisms. The models relate disease dynamics to basic cell parameters, such as proliferation rate (number of cell divisions per unit of time) and self-renewal fraction (probability that a progeny of a stem cell is again a stem cell). Motivated by the recent findings, we extend the models to take into account competition of multiple leukemic clones. Depending on the posed questions, we use different mathematical approaches to study clonal selection in presence and absence of therapy. These include nonlinear ordinary differential equations, integro-differential equations and stochastic simulations.

A combination of mathematical analysis, computer simulations and patient data analysis provides insights into the following clinically relevant questions: (1) Which mechanisms allow leukemic cells to out-compete their benign counterparts? (2) How do leukemic stem cell parameters (proliferation rate and self-renewal fraction) affect the clinical course and patient prognosis? (3) How do leukemic stem cell parameters affect clonal competition? Which parameter combinations confer selective advantages? (4) How do leukemic stem cell parameters impact on the topology of the clonal hierarchy? (5) How do nonlinear feedback signals affect disease dynamics and treatment response?

The talk is based on joint works with Anna Marciniak-Czochra, Jan-Erik Busse (Institute of Applied Mathematics, Heidelberg University), Anthony D. Ho, Natalia Baran and Christoph Lutz (Heidelberg University Hospital).

Nicolas Vauchelet (Université Paris 13)

Mathematical modeling of the spread of Wolbachia for dengue control.

Bacteria Wolbachia has gain a lot of attention since scientists discover that infected mosquitoes with this bacteria cease to transmit some disease like dengue, chikungunya and Zika. Moreover, this bacteria is maternally transmitted from mother to offsprings. Then a strategy of control of dengue transmission consists in releasing Wolbachia infected mosquitoes in the aim to replace to natural population of mosquitoes by infected mosquitoes. In this work, we are concerned with the spatial spread of Wolbachia infected mosquitoes into a host population. We focus on the two following questions: How the spatial repartition of the releases will influence the spread of the bacteria into the population ? Once the spread is initiated, is it possible that environmental characteristics stop the spread ?

Vuk Milisic[1] and Dietmar Oelz[2]

Mathematical analysis of adhesion forces in the filament based lamellipodium model.

In this talk we present the mechanical model of the lamellipodial actin-cytoskeleton meshwork. The model is derived starting from the microscopic description of mechanical properties of filaments and cross-links and also of the life-cycle of cross-linker molecules [8, 7, 1, 2]. We introduce a simplified system of equations that accounts for adhesions created by a single point on which we apply a force. We present the adimensionalisation that led to a singular limit motivating our mathematical study. Then we explain the mathematical setting and results already published [3, 4, 5]. In the last part we present the latest developments : we introduce the space dependence and show how to include it in the model, we sum up asymptotic results available in this context and we give new results for the fully coupled system with unbounded non-linear off-rates [6].

References

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Talks

Electromechanical Modeling of Cardiac Activity : Existence Results for a Physiological Ionic Model.

Mostafa Bendahmane[1], Fatima Mroue´[2,3], Mazen Saad[2], Raafat Talhouk[3]

[1]Institut de Mathématiques, Université de Bordeaux, Bordeaux, France
[2]Ecole Centrale de Nantes, Laboratoire de Mathématiques Jean Leray, Nantes, France
[3]Laboratoire de Mathématiques, EDST, Université Libanaise, Hadat, Liban

The contraction of the heart is initiated by an electrical signal called action potential. Electrical stimulation of the cardiac myocytes leads to their depolarization and subsequently to their contraction. The propagation of the electrical signal is widely described at the macroscale by the Bidomain model. Still at the macroscopic level, cardiac deformation can be modeled by the equations of motion for a hyperelastic material, written in the reference configuration. Furthermore, its contraction is influenced by intrinsic mechanisms taking place at the microscopic level. In our work, we take this ability into account following the active stress formulation where the deformation gradient is factorized into active and passive factors.

In this talk, we discuss the well posedness of an electromechanical model of the heart coupled with a physiological ionic model. The proof is based on a Faedo-Galerkin method followed by compactness argument.

Keywords : Electromechanical coupling, Bidomain Equations, weak solution

Lung volume VS air flow :
a match for shear stresses distribution in the bronchial tree.

Jonathan Stéphano
Université de Nice Sophia Antipolis

Abstract

The lung is a vital organ that is able to protect itself from external pollutants thanks to two main mechanisms: cough and a mucus barrier that is constantly renewed and cleared up the bronchial tree. These systems can however have malfunction and chest physiotherapy is then a common treatment to prevent mucus stagnation and potential development of infections. Many techniques of chest physiotherapy rely on the interaction between an high air flow and mucus. Air flow induces a shear stress, which, if high enough, is able to liquefy and to motion mucus [1,2,3]. Mean shear stress in a bronchus is proportional to the ratio between mean air velocity in the bronchus and the radius of the bronchus. Thus two possible chest physiotherapy techniques to motion mucus are possible: either to work at normal lung volume and to create a strong air flow (high air velocity with normal bronchi radii); or to work at small lung volume and to use relatively small airflows (low air velocity with small bronchi radii). Both techniques are hypothesised to bring an high shear stress on mucus, but no precise scientific understanding of the underlying biophysics involved exists as of today. The response of bronchi to their environmental pressure [4] and the pressure response of the lung to its volume [5] are both non linear, hence the induced shear stress and the response of mucus to these two techniques are not easily tractable and are probably different.

In this work, we propose a quasi-static model that is able to predict shear stresses distribution along a model of the bronchial tree as a function of air flow in the lung and an homogeneous pressure on the chest. The model's equations are solved numerically. Our model predicts that shear stress reaches a maximum in a specific generation in the bronchial tree and that the position of the maximum depends on the amount of air flow and chest pressure. Our results suggest that the tuning of both lung volume and amount of air flow might allow to maximise the motion of mucus in a specific depth in the lungs.

This work is supported by CNRS, ANR VirtualChest (ANR-16-CE19-0014) and the Vader center
(IDEX UCA JEDI).

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[5]: **Agostini & Hyatt**, 2011, Comprehensive physiology III

Mathematical model for sequential patterning of tooth signaling centers.

Monika Twarogowska, ENS-Lyon, France

in collaboration with **S. Pantalacci** and **V. Calvez**

In this talk we focus on the behavior of signaling centers responsible for tooth patterning in the growing mouse jaw. Patterning is usually seen as a straightforward process, rather than a dynamical process that could take circuitous routes. However, experimental studies of dynamics of Edar gene expression show that patterning of the first mouse molar M1 involves what is called a developmental palimpsest - patterns are established, erased by activation waves and remodeled again into new patterns. Recovering from this palimpsest, R2 vestigial tooth germ and the first molar signaling center co-exist in the upper jaw and fuse into a single large signaling center in the lower jaw.

We present a mathematical model of these complex behaviors (pattern formation/erasing, fusion), which is based on simple mechanisms. The model is of reaction-diffusion type and describes concentrations of an activator and its inhibitor on a growing domain. Its crucial feature relies on the observation that Turing patterns and traveling wave propagation can arise from the same kinetic reactions system up to the change of one parameter. We use tissue maturation to switch between a bistable system (wave-like patterns) in the immature area and a stable system (Turing-like pattern) in the mature area. The possible fusion of SC is considered as a secondary effect on a mature, non-growing tissue, and is mediated by chemotaxis signaling and cell migration.

We show numerical results for wildtype R2-M1 dynamics and for Edar mutant development, where paradoxically due to enhanced inhibition the palimpsest of R2 does not occur and this signaling center persists. Our work provides the first theoretical framework to understand the complex dynamics of molar row formation and expands our view of mechanisms enabling sequential pattern formation.

Gala Dinner – Wednesday June 20th at 8:00 pm

Restaurant "Le 1"

1 Rue Olympe de Gouges, 44200 Nantes

Map 3

The restaurant « Le 1» is located close to the tramway line 1 (8mn walk)

stop : Médiathèque

June 21th « fête de la Musique » everywhere in Nantes

Best places for listen jazz :

Le Melocotton 9, rue de l'heronnière 44000 Nantes (close to Place Graslin) 6:30 pm to midnight

Le Pannonica 9 rue basse-porte 44000 Nantes (close to marché de Talensac) 8:30 pm to midnight

https://www.nantes-tourisme.com

Château des Ducs de Bretagne
4, Place Marc Elder 44000 Nantes
Phone +33 (0) 811 46 46 44

Passage Pommeraye
rue de la Fosse
44000 Nantes
Phone +33 (0)2 40 48 78 17

Les Machines de l'île
Parc des Chantiers
Bd Léon Bureau
44200 Nantes

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