LIST OF ONGOING COLLABORATIVE PROJECTS

METABOLIC REPROGAMMING OF CANCER STEM CELLS: A STOCHASTIC MODELLING APPROACH

Advisors: Dr. Tomás Alarcón (Computational & Mathematical Biology Group, CRM)

Co-advisor: Dr. Javier A. Menendez (Metabolism & Cancer Group, Translational Research Laboratory, Catalan Institute of Oncology)

Fellow: Núria Folguera

Project Description. For over thirty years, research in oncology has been dominated by a genocentric approach where targetted therapies, i.e. drugs developed to interfere with specific cancer gene products have been the focus and ultimate aim of cancer biology. Advances in genomics and other cancer-omics (proteomics, epigenomics, etc.) have further boosted this approach. However, the success of this approach in terms of the development of new, efficient cancer drugs has felt short of expectations.

Complementary to this view, one may hypothesise that the time is ripe for revisiting Otto Warburg's simple model for cancer which states that the prime cause of cancer is the replacement normal cell metabolism (cellular respiration, oxidation of sugar) by a metabolism based in fermentation of sugar, particularly in the light of recent results hinting at the role of cancer metabolism as a molecular gatekeeper of the conversion of somatic cells into cancer stem cells, whereby metabolic reprogamming of cancer stem cells appears as a key feature of the evolutionary dynamics of cancer cell populations, and alternative to the genocentric cancer therapy can be proposed where creating cellular metabotypes that hinder the occurrence of cancer stem cell become therapeutic target.

Aims and objective: The overall aim of this project is to analyse in detail the stochastic dynamics of cellular reprogramming under metabolic constraints, and based on its principles, formulate strategies that allow us to control the occurrence of cancer stem cells. More specifically, we aim to:

- Characterise the effects of cancer metabolism on the stochastic dynamics of the gene networks that regulate the transition between pluripotency and differentiation.
- Formulate stochastic multi-scale models which allow us to incorporate our models of the pluripo- tency gene regulatory network in models of the dynamics of cell populations, in order to compare the population dynamics results generated by these gene regulatory network models with

experimental results and study optimal therapeutic strategies to avoid the populations generated by cancer stem cells to thrive.
- Analyse repositioning of current drugs known to affect metabolism as cancer drugs.

Methodology: This project aims to formulate a new description of the evolutionary dynamics of cancerous cell populations with metabolic reprogamming of cancer stem cells. We will use the theory of continuous-time Markov processes to formulate and analyse the dynamics of the reprogramming gene regulatory network. Once these are formulated, we will use stochastic multiscale methods to incorporate our model of the gene regulatory network into a population dynamics model, which will allow us to study the evolutionary dynamics of the competition between normal and cancer cells as well as modelling different therapeutic strategies.

MODELLING THE GROWTH OF KIDNEY CANCER: A HYBRID MULTISCALE-IMAGE ANALYSIS APPROACH

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Co-advisors:	Dr. Anna Messeguer (Vall d'Hebron Research Institute) Dr. Joan Morote (Head of Urology, Vall d'Hebron Hospital)
Fellow:	Juan Calvo

Project Description. For over the last twenty years, angiogenesis has been one of the focal points of oncological research. Angiogenesis is the process whereby new blood vessels are generated by sprouting off from the existing vasculature. Whilst angiogenesis occurs in normal physiological situations, it can be hijacked by a solid tumour in order to secure access to nutrients and other resources and thus grow at the expense of the organism and eventually replacing the normal tissue. Most solid tumours are angiogenic, however among them, kidney cancer is considered ones of the most prone to develop angiogenesis.

Kidney cancer is the seventh most common cancer in the USA and the UK and it is commonly treated by means of surgical resection of the tumour. However, physicians must often make a judgement call as to whether operating is worth, as kidney tumours may grow slowly and not pose an immediate threat. In particular, when this disease affects the elderly, unnecesary operations cause great discomfort, as well as costs for the health system. The aim of this project is to provide a tool for physicians to support the clinical decision. This tool will be based on a multiscale model of tumour growth aimed at predicting tumour progression. The model will be trained on a retrospective data base of medical acquisitions feed with clinical measurement extracted by medical image analysis. The results of the model will be correlated with blood analysis.

Aims and objectives. The overall aim of this project is to produce a multiscale of kidney cancer and angiogenesis which will be parametrised and trained by means of image analysis. More specifically, we aim to:

- Formulate a multiscale of tumour growth and angiogenesis specific to kidney tumours.
- Calibrate and train the abovementioned model by extracting by image analysis relevant measure-ments obtained by means of image analysis from non-invasive acquisition of patients. Eventually, the objective is to provide physicians with a tool that will support the clinical decision-making regarding whether or not is necessary to operate a patient.

- Correlate the result of the model with blood analysis bio-markers for early cancer detection.
- Use the model to predict the effect of specific drugs targetting signalling pathways specific to kidney tumours.

Methodology. This project aims to formulate a new description of the growth of kidney tumours. We will use the techniques of multiscale modelling of tumour growth and angiogenesis, in which mathematical models of different tissue compartments (normal tissue, cancer cells, vasculature, etc.) are coupled by means of partial differential equation models for the concentration of nutrients (e.g., oxygen) and signalling cues (e.g., angiogenic factors). This multiscale model will be calibrated and, then, trained to predict the evolution of the growing kidney tumours by using image analysis techniques applied to non-invasive medical acquisitions.

STATISTICS, MODELS, AND PREDICTION OF SYNTHETIC EARTHQUAKES

Advisors: Dr. Álvaro Corral (CRM, Barcelona)

Co-advisor: Dr. Eduard Vives (Universitat de Barcelona)

Fellow: Isabel Serra

Project Description. Prediction of earthquakes has unveiled as an almost impossible task. Decades of intensive efforts have not yielded any significant success. In addition to the enormous complexity of tectonic processes, one of the reasons of the failure is the unaccessibility of the Earth's crust. In this project we plan to get deep understanding in these problems by the study of the synthetic earthquake-like events that take place in controlled fracture experiments [1,2].

As a first step, the statistical analysis will test the validity or not of the main laws of statistical seismology in the synthetic events, relating space, time, energy, and their correlations. Fitting, goodness-of-fit tests, scaling analyses, and declustering algorithms (in particular based on complex-network theory) will be necessary tools to apply and develop here.

A second task will consist of the development of models for the occurrence of the synthetic events. The simplest approach will deal with stochastic point processes incorporating the main laws of statistical seismology, in order to verify how all these laws are compatible between them. The key idea is "triggering": any event (even small ones) can trigger other aftershock events and so on, generating cascades or avalanches of events. Despite the simplicity of this modeling, the existence of cascades endows the problem with a great mathematical complication. Another level of modeling goes to more microscopic, fundamental processes, using simple cellular automaton models to reproduce the branching nature of fracture processes and the interplay with the processes of fault generation. It is expected that these models will be helpful in the task of prediction of the most extreme events.

The outcomes of the proposed project would have wide applicability in the understanding of the occurrence of real natural earthquakes, induced (artificial) seismicity, as well as in the collapse of human-made structure such as mines and buildings.

The selected candidate (mathematicians, physicists, engineers...) should have a good academic profile, strong motivation to do cross-disciplinary research at all levels (experiments, computer simulations, data analysis, and theoretical work), and high sensibility towards the risks posed by natural hazards.

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THE QUANTITATIVE LAWS OF MUSICAL DISCOURSE: MODELS AND APPLICATIONS

Advisor: Dr. Álvaro Corral (CRM, Barcelona)
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Fellow: Maria Isabel Moreno

Project Description. It is intuitively obvious that music is neither "regular" nor random or chaotic. Rather, it seems to keep a delicate balance between predictability and surprise that clearly attracts our attention (even if we are well aware of the musical piece). Not much research has unveiled the fundamentals of this situation. In fact, the systematic mathematical study of these properties is just starting to take place [1].

In this project, we propose a comprehensive characterization of the structure of musical discourse from the perspective of statistics, nonlinear time-series analysis, stochastic processes, network theory, and complex-systems science. Both, audio databases and symbolic scores in electronic form (such as MIDI) will considered to perform a large-scale big-data study, encompassing classical, jazz, and modern pop music (among others). Several empirical laws found in other complex systems, such as the Zipf's law, will be tested, and diverse sorts of models will be tried in order to reproduce the empirical findings, from which important applications can also arise (like the identification of plagiarism or enhancing music recommendations for end users). Special attention will be paid to the dynamics properties of the complex network defined by the transitions between successive "musical words" [2], for which new tools in the mathematics of networks will be necessary to develop.

The ideal candidate (mathematicians, physicists, statisticians, computer scientists...) should have a good academic record, a natural curiosity to raise and explore new issues, and high motivation to do cross-disciplinary research. Good computer programming skills are compulsory. Some knowledge of music will be appreciated but it is not necessary to start the project.

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MATHEMATICAL MODELLING OF BIOLOGICAL EVOLUTION: THE DEVELOPMENT OF SPECIALIZATION AND THE UNIVERSALISM, AND THE APPEARANCE OF SPECIES

Advisor: Dr. Andrei Korobeinikov (CRM, Barcelona)

Co-advisor: Dr. Santiago F. Elena (Evolutionary Systems Virology Group, IBMCP (CSIC-UPV))

Fellow: Anel Nurtay

Project Description. The objective of this project is study of the biological evolution and the appearance of biological species. In particular, a hypothesis with will be verified is that a possible route for the appearance of new biological species is via the development of specializations; that is, the adaptation for a better exploiting of a particular niche at the expenses of demoting the ability of exploitation other niches. The other hypothesis that will be studied is that the universalism (that is the ability to efficiently exploit a few niches) gives an advantage, and hence has a chance to arise and develop, is the supply of resources in specific niches is volatile.

We consider viruses as a case study. Due to their simplicity, viruses can serve as an excellent model in Evolutionary Biology. To verify the above mentioned hypothesis, we have to construct a mathematical model of viral evolution, which should be able to describe the development of specialization. This model is to be based on the Nowak-May model of HIV and would be a further development of a model of viral evolution suggested by A. Korobeinikov and C. Dumpsey [1]. In the model that will be developed, viral subtypes should be represented in a two-dimensional continuous phenotype space. In such a phenotypes space, without loss of generality the random mutations can be modelled by diffusion.

To study the development of specialization, two symmetrical niches should be defined as local maximum of the fitness landscape. (Here the fitness can be described by the probability for a single varion to infect a target cell.) In this model framework, the niches correspond to two different types of target cells or host bacteria. Virus is assumed to be placed in an environment where there would be simultaneous and symmetric access to both biological niches.

As a specific and practically relevant problem, we plan to use this model to study the development of specialization, as well as development of the resistance to immune response and to drug, in HIV-1.

References

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MATHEMATICAL MODELLING OF NANOPARTICLE EVOLUTION

Advisor: Dr. Tim Myers (CRM, Barcelona)

Co-advisor: Dr. Victor Puntes (Institut Català de Nanotecnologia)

Fellow: Helena Ribera
Vincent Cregan

Scientific description. The goal of this project is to develop and analyse mathematical models of the growth or shrinkage of nanoparticles. The initial work will build on mathematical models of melting at the nanoscale, already developed within the industrial mathematics group at the CRM [1]. This work involves solving heat equations coupled to a phase change model, using approximate analytical and numerical methods. The project will be linked to experiments carried out at the Institut Català de Nanotecnologia, see `www.inorganicnanoparticles.net`.

Motivation. Nanoparticles have a vast array of applications in medicine, environmental remediation, new materials and energy [2]. In medicine, they can be used to improve diagnosis and therapy, as drug delivery agents, or as active principles. For example, cerium oxide particles are used as anti-oxidants to remove oxygen free radicals from the bloodstream after a traumatic injury. They can also decrease inflammation (chronic inflammation induces cancer) in a non-biological way, so that it does not interfere and affect the biological system. Due to its chemical stability and optical properties gold is perhaps the most common material for nanoparticles. It is used in drug delivery systems, hyperthermia treatments and as a contrasting agent in medical imaging. Thanks to their size, which corresponds to the size of biological macromolecules, proteins, DNA etc, there are many other potential medical uses of nanoparticles including starving cancer cells, treatment of leukemia, increasing bone growth, injecting drugs through cell walls, slowing down aging and clot busting.

In certain circumstances it is important that after fulfilling their role the particles disintegrate and dissolve into individual molecules or small groups which are easily expulsed from the body. At other times it is desirable for them to clump together. A current problem with the use of cerium oxide as an anti-inflammatory is that the particles grow and so become less effective. Understanding the growth or shrinkage of nanoparticles is therefore key to design and engineer their successful use.

During the term of the project it is intended to build on the existing work at the CRM in the modelling of nanoparticle growth and subsequently to extend this to:

- Ostwald ripening: a process where large particles grow by consuming smaller particles [3].
- The nano-Kirkendall effect: a enhanced diffusion process where, with relation to the current project, a silver nanoparticle coated with gold can exhibit silver diffusion so that after a few hours all that remains is a hollow gold shell [4,5].

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BOILING CRISIS

Advisor:	Dr. Tim Myers (CRM, Barcelona)
Co-advisor:	Dr. Eduard Vives (Faculty of Physics, University of Barcelona)
Fellow:	Vincent Cregan

Scientific description. When a fluid lies on a hot surface various phenomena can occur, depending on the surface temperature. At relatively low temperatures the fluid simply convects and removes heat from the surface. Increasing the temperature boiling begins, where isolated bubbles form at nucleation sites on the solid surface. As the temperature increases further the bubbles begin to join together. This regime still removes a lot of heat from the surface. However, at a certain point the bubbles join to form a vapour layer whilst at the same time the heat transfer coefficient decreases rapidly, which may allow the surface temperature to increase dramatically. This is a vital issue in the cooling of nuclear power plants (see Wikipedia: Three mile Island accident; Chernobyl disaster).

This project will build on previous work of the industrial mathematics group at the CRM on phase change and fluid flow. The focus will be to investigate the various regimes of boiling in order to understand the crisis regime.

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WAVELETS-BASED METHODS TO COMPUTE SOLUTIONS OF BSDES ARISING IN FINANCE

Advisor: Dr. Luis Ortiz-Gracia (CRM, Barcelona)

Co-advisor: Dr. Cornelis W. Oosterlee (Centrum voor Wiskunde en Informatica, Amsterdam)

Fellow: Gemma Colldeforns

Scientific description. In recent years, *backward* stochastic differential equations (BSDEs) have received more attention in financial mathematics. Whereas the theory and applications of classical *forward* stochastic differential equations (FSDEs), with a prescribed initial value, is traditional and became widely known, we are concerned along this project with BSDEs. A BSDE is a stochastic differential equation for which a terminal condition, instead of an initial condition, has been specified and its solution consists of a pair of processes.

Market imperfections, such as different lending and borrowing rates for money, the presence of transaction costs, or short sales constraints, give rise to more involved nonlinear BSDEs. Moreover, the Black-Scholes formula for pricing options can be represented by a system of decoupled forward-backward stochastic differential equations. If the asset price follows a jump diffusion process then the option can not perfectly be replicated by assets and cash, i.e., the market is not complete. A way to value and hedge options in this setting is by utility indifference pricing, where a certain utility value is assigned to the possible profits and losses of the hedging portfolio. The pricing problem can be solved by means of a BSDE with jumps.

The well-known Feynman-Kac theorem gives a probabilistic representation for the solution of a linear parabolic partial differential equation (PDE) by means of the corresponding FSDE and a conditional expectation. The solution of a BSDE provides a probabilistic representation for *semi-linear parabolic PDEs* which is a generalization of the Feynman-Kac theorem. Also the converse relation holds. This connection enables us to solve semi-linear PDE by probabilistic numerical methods, like Monte Carlo simulation techniques.

Probabilistic numerical methods to solve BSDEs may, for example, rely on time discretization of the stochastic process and approximations for the appearing conditional expectations. Least square Monte Carlo regression to approximate the conditional expectations has been used and a rich literature exists on other methods, for example based on chaos decomposition formulas or binomial trees.

In this project, we propose a new method to approximate the solution backwards in time. This approach is based on the Wavelet Approximation (WA)

method, which was originally developed for computing credit portfolio losses and also for the robust pricing of European options. The method is based on Haar wavelets expansions and relies on the characteristic function of the transitional density. The characteristic function is in principle available for Lévy processes, or affine jump diffusion processes. The applicability of the resulting method should be therefore quite general. We aim to explore the connection to stochastic control problems in Economics and Finance, to the Bermudan option pricing framework and Credit Valuation Adjustment (CVA) concepts, among other interesting applications in Finance.

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THE DYNAMICS OF UP- AND DOWN-STATE ACTIVITY IN THE CEREBRAL CORTEX

Advisor: Dr. Alex Roxin (CRM, Barcelona)

Co-advisor: Dr. Jaime de la Rocha (IDIBAPS)

Fellow: Narani van Laarhoven

Background. One of the most striking differences in the activity of the cerebral cortex between the waking and sleeping states is the appearance of slow ($\sim$ 1Hz) spatially synchronized fluctuations during so-called slow-wave or non-REM sleep. This slow-wave activity is characterized by an alternation between periods of relative neuronal silence during which neurons are strongly hyper-polarized, known as down-states, and periods of neuronal activity which closely resembles that seen in the awake behaving animal, known as up-states. Since up/down state activity was first discovered twenty years ago it has been intensively studied and characterized in cats, rats and other mammals through electrophysiological techniques. At the same time, modelling efforts have attempted to reproduce the basic phenomenology of up/down state activity. However, despite the large body of experimental and theoretical work, many questions regarding the physiological and dynamical mechanisms underlying up/down state activity remain. In particular, experimental data provide strong constraints on key features of the dynamics including: the irregularity and heterogeneity of spiking activity, the structure of pairwise correlations in spiking activity, and the duration of and irregularity in switching times between up-state and down-states. Nonetheless, there is currently no computational model which can self-consistently incorporate all of these experimental constraints.

Project Description. The PhD candidate will be involved in a collaborative effort between the Computational Neuroscience Group (CNG) at the Centre de Recerca Matemàtica (CRM) and the Cortical Circuit Dynamics Group (CCDG) at the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) to elucidate the dynamical and physiological mechanisms underlying up/down state activity in the cerebral cortex. Specifically, electrophysiological data collected from *in-vivo* experiments with rats in the CCDG will be used to constrain computational models developed by the candidate in collaboration with the PIs of both groups. Simulations of large-scale networks of spiking neurons will be directly compared with electrophysiological data, while an array of mathematical techniques will be brought to bear on simplified meanfield models of up/down state activity in order to pin down and characterize the fundamental dynamical mechanisms of importance.

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THE NEURAL BASIS OF STOCHASTIC BEHAVIOR

Advisor: Dr. Alex Roxin (CRM, Barcelona)

Co-advisor: Dr. Jaime de la Rocha (IDIBAPS)

Fellow: Genis Prat

Introduction. Although the survival of animals depends on their ability to reliably respond to situations threatening their survival (e.g., the presence of a predator or a prey), when looked closely, behavior can be described in many aspects as stochastic. Subjects responding for instance with a button press every time they detect a cue on a computer screen, exhibit large variability from repetition to repetition in the response reaction time and in the exact motor movement of the arm. In one hand, this is not so surprising given that brain activity is based on the kinetics of ion channels in the neurons membrane that are affected by thermal noise. Thus, processes at the cellular level (microscopic description) such as synaptic transmission between neurons can be quite unreliable. On the other hand, the brain contains billions of neurons and computations driving behavior rely on the activity of thousands of cells. Assessing the impact of fluctuations observed at the microscopic level on observables at the macroscopic level it is however not a simple task. In principle one could expect that independent sources of noise in each cell would be averaged out such that signals at the network level would be reliable. Given that the behavior of the global system is stochastic, it must be therefore because the sources of variability at the single cell level are correlated. This is in fact is generally observed when pairs of neurons are recorded simltaneously: their Poisson like spiking stochasticity is correlated.

In the last twenty years theoretical neuroscientist have used mathematical models to investigate how neuronal networks composed of a large number of neurons can generate stochastic activity. Current models of cortical circuitry are capable of reproducing the stochasticity at the single cell level (i.e., Poisson like spike trains) in the absence of any external source of noise. It has been recetly shown however that these same models generate negligible correlations among neurons. This implies that the stochastic firing of each cell can be averaged out to obtain non-variable population signals and reliable macroscopic computations. Thus, we still do not understand how to build large neural networks which can generate a structure of pair-wise correlations to that found in the cortex. Understanding the mechanisms underlying stochastic behavior might imply therefore understanding what these neuronal correlations mean and how they are generated.

Objectives. The objective of this project is to understand the neural basis of the behavioral stochasticity exhibited by subjects on simple decision-making tasks. For this we will combine:

(1) Psychophysical experiments characterizing the behavioral stochasticity of subjects in a simple perceptual task.
(2) Mathematical modeling of neuronal networks that implement a categorization task and can reproduce that behavioral stochasticity found in the data.

Methodology. We will design a two-alternative forced-choice (2AFC) discrimination task where human subjects need to make binary categorical decision about the spectral content of a broad band acoustic stimulus. Experiments will be carried in the laboratory of Jaime de la Rocha (IDIBAPS) in an acoustically controlled environment. The task will be implemented and controlled by a computer program coded in Python. The program will present a sequence of auditory stimuli with various levels of categorization evidence and will and record several aspects of the response in each repetition (choice, reaction time, response motor movement using a computer mouse, response confidence reported by subject). Behavioral analysis of these variables will be carried out off-line. We will investigate the relation between task performance (fraction of correct responses), reaction time, consistency (variability in the response to identical stimuli) and confidence. We will characterize psychophysical kernels to characterize the dynamics of evidence integration across the stimulus duration.

We will model decision-making networks at two levels of description. First we will study phenomenological models of sensory integration and decision-making. In particular we will analytically characterize the behavior of the Drift Diffusion Model (DDM) [1, 3]. This is a canonical mathematical model commonly used to characterize the behavior of during two-choice decision tasks, which despite its simplicity, can reproduce several features generally found in this class of psychophysical tasks (e.g., speed-accuracy trade off). The relation between the various behavioral statistics described above will be characterized using the DDM. Second, we will build a network composed of spiking neurons which can implement binary categorization of noisy input stimuli [2, 4, 5]. We will investigate the mechanisms generating choice variability compatible with our experiments using mean-field analysis and numerical simulations. We hypothesize that in order to produce stochastic macroscopic behavior the network must operate near a bifurcation to be able to amplify microscopic fluctuations and impact the global behavior.

Our project will serve to understand the impact of neuronal variability in decision-making and to reveal basic dynamical principles underlying the computations perform by the nervous system.

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