Scientific project submitted in 2012

2. Research Project of the NeuroMat Proposal

2.1 Description of the scientific and technological issues to be addressed

The fast evolution of neuroscience is producing huge masses of data and a host of new phenomena revealed by novel experiments and interventions. This progress, however, is not accompanied by similar advances in theoretical understanding. The resulting situation has been nicely described as data-rich yet theory-poor in the home page of the Redwood Center for Theoretical Neuroscience. Mathematics is indispensable to break this imbalance.

A first scientific challenge is posed by the complexity of the databases. Current mathematical tools are insufficient for its size and high dimensionality. New procedures must be devised that are both statistically accurate and computationally feasible.

However, a second, deeper challenge arises from the apparent randomness displayed by neuronal data. As stated in a recent publication:

Experimental data suggests that neurons, synapses and neural systems are inherently stochastic [. . .]. In fact, several experimental studies arrive at the conclusion that external stimuli only modulate the highly stochastic spontaneous firing activity of cortical networks of neurons [. . .]. Furthermore, traditional models for neural computation have ben challenged by the fact that typical sensory data from the environment is often noisy and ambiguous, hence requiring neural systems to take uncertainty about external inputs into account. (Buesing et al., 2011).

The mathematical description and treatment of neural phenomena requires, thus, a probabilistic setup. Furthermore, neural data are collected at very different scales —from unitary recordings to mesoscopic brain regions to behavioral measurements. The stochastic framework must, therefore, be able to integrate data of very different nature and provide mechanisms to pass information from one scale to the next.

A striking illustration of all these features is the phenomenon of neural plasticity. This is the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections (Cramer et al., 2011). It is a crucial feature, responsible of processes such as learning and memory, which drives the response of the nervous systems to illness and injury. Plasticity phenomena have already been extensively documented at the molecular, synaptic, cellular, network, and systems levels (Cramer et al., 2011). However, as stated in Nudo (2006),

While these new findings in the past 20 years have been exciting, these events still represent little more than correlative phenomenology, at least with respect to understanding how the brain recovers function after injury.

A new, solid theoretical approach is obviously needed. Such an approach could help distinguish between normal and altered neural dynamics and lead to a deeper understanding of the mechanisms underlying neurorehabilitation. Advancement in this direction might guide the development of novel interventions. The new understanding and techniques generated by the Center should also contribute to the analysis of altered neural states deriving from brain injury.

The general goal of the proposed Center is the development of a mathematical framework for neuroscience, based on the premise that neural states are probability measures in suitable measure spaces. This identification, which applies at all scales or levels of study, is the key for the theoretical analysis of neural phenomena and, in particular, for the development of the new statistical and computational tools needed to treat neural data. This probabilistic framework must be constructed so as to fulfill a number of requirements:

1. It must rely on all relevant areas of mathematics. It must involve, not only researchers in probability and statistics, but also specialists in other areas such as combinatorics, graph theory, rigorous statistical mechanics and development and analysis of algorithms.
2. It must lead to models helping to understand the actual phenomena, and not just to convenient phenomenological descriptions. This type of descriptions —obtained through the combination of high computational power and standard statistical techniques— is clearly insufficient to tackle the complexity of the phenomena. The understanding of neural phenomena is much more than the application of data-mining techniques. Careful mathematical analysis, developed in collaboration with neuroscientists, is needed.
3. It must rely on original lines of attack, tailored to neural phenomena. Previous attempts to mathematically model this phenomena —some of them by well known mathematicians— relied instead on importing known stochastic approaches, mainly from statistical mechanics. This strategy has been shown to be inadequate and did not produce significant contributions to the field (see comments by Friston et al., 2010; Truccolo, Hochberg and Donoghue, 2010; Cessac, 2011). New mathematical paradigms must be devised.
4. It must lead to efficient algorithms and procedures that can be put to use and confronted with data. These algorithms will be the result of the new probabilistic models and statistical procedures developed in the Center. To this end, the Center will foster the combined effort of probabilists, statisticians, computer scientists, rehabilitation clinicians and neuroscientists.
5. It must be subjected to frequent and merciless testing against experimental information. Hence, the NeuroMat Center will associate mathematicians with experimental neuroscientists and physicians.

The new mathematics will be applied to neural phenomena at the frontier of current research. The NeuroMat project aims to achieve what previous approaches —data mining and naive mathematical adaptation of existing paradigms— failed to accomplish. It will rely on the extensive experience of many of its members on the rigorous treatment of other complex human phenomena, such as language acquisition and change (see, e.g., Galves et al., 2012).

The following quote, from the acceptance speech of the illustrious mathematician Mikhael Gromov for the 1999 Balzan price, summarizes, in fact the mission of the Center:

The task of mathematics and mathematicians is to articulate the visible regularities in the physical and mental worlds, and to find new structural patterns that can not be perceived by direct intuition and common sense.

To develop the mathematics needed to find regularities, patterns and laws in neural phenomena is the mission of NeuroMat.

2.2 How the scientific activities of the Center relate to the state of the art

NeuroMat is designed to be at the scientific level of the major institutes on theoretical neuroscience being created in different countries as a response to the importance and timeliness of the topic. Following the international pattern, NeuroMat, while being a mathematics institute, has a definite interdisciplinary character, bringing together mathematicians, computer scientists, neuroscientists and rehabilitation clinicians to handle mathematical theory, neural questions and experimental data in an integrated fashion. Through this combined approach the Center will address frontier issues in neural research with the aim of obtaining significant advances.

While Brazil has many excellent groups collecting neural data and performing daring experiments and interventions, no institute for theoretical neuroscience has yet been proposed. This Center is, therefore, a natural addition to the Brazilian scientific scenario aimed at correcting this imbalance. Its creation is fostered by the fortunate fact that the State of São Paulo counts with a group of researchers specially qualified for the task.

Indeed, the team of mathematicians at the origin of the proposal has recognized expertise in the required mathematical ingredients —probability and statistics, mathematical statistical mechanics, analysis of algorithms and combinatorics, — and extensive experience in interdisciplinary studies, including theoretical and experimental work in linguistics. Their proficiency has been recognized through many State, Federal and Binational grants —including a prestigious USP research grants (Mathematics, Computation, Language and the Brain, R$ 1.998.000,00), and by the large number of distinguished international researchers taking part in their projects. The team is at the origin of the Núcleo de Modelagem Estocástica e Complexidade (NUMEC) hosted by the Universidade de São Paulo. This center has completed almost ten years of intense activity in the study of stochastic collective phenomena, leading to a solid and original scientific production, to the trining of young researchers and to a extended network of international connections. For the present project, this mathematic team is associated with a group of neurobiologists and rehabilitation clinicians, themselves recently rewarded with an important USP research grant (New Approaches in Brain Injury Rehabilitation: Development and Assessment, approx. R$ 900.000,00).

2.3 How the strategy of the Center will impact in a significative way the domain of research

The strategy of the Center is to use all the power of rigorous mathematics to address in an innovative way central issues in neuroscience: the ubiquituous phenomena of neuroplasticity, learning processes, motor planning and memory consolidation. Advances in these issues will have a major impact in neuroscience, and, at the same time, help create a new mathematical area in the interface of probability theory, combinatorics and statistics.

Neural phenomena involve activity at micro, meso and macro levels. Surprisingly, while at micro and meso levels these phenomena seem to display an inherent randomness, many macro phenomena are fundamentally predictable. To reconcile this apparent contradiction and to achieve an insightful formulation of the phenomena, the Center proposes a novel probabilistic framework based on the premise that neural dynamics can be described, at all scales, by stochastic processes taking values in suitable configuration spaces. This provides a uniform framework for the simultaneous consideration of the different scales and the connections between them. Such an approach should provide a two-way link between neuronal activity and animal behavior.

This link, however, has to be properly understood. Indeed, experiments show that in general a given animal behavior does not correspond to an unique realization of neuronal activity. The conjecture put forward by the Center, instead, is that each type of animal behavior relates to a specific probability distribution on the set of neural activity realizations. These realizations are defined not only by the ensemble of spike trains but also by the time evolving functional interactions.

A probabilistic —statistical-mechanics inspired— approach was first proposed in the eighties by a number of well known mathematicians. The approach did not have a lasting influence in neuroscience, probably because it was based on the direct importation of statistical mechanical ideas without adequate data to confront the proposed stochastic multi-component models. Data has become plentiful since then, due to the development of techniques for simultaneous recording at different levels, e.g. multi-unitary recording, optical imaging techniques, fMRI and multi-channel EEG.

The treatment of these new data posed a major scientific challenge that was initially met through the combined use of large computer resources and descriptive statistics. At the same time, the new field of computational neuroscience was created (see, e.g., the references in http://bluebrain.epfl.ch/), devoted to numerical simulation of systems comprising very large neuronal populations, starting from detailed modeling of individual neurons and conductances. Understandably, this intensive computational approach has intrinsic limitations to reproduce complex phenomena at the level of physiology and behavior. More importantly, this approach does not lead to a parsimonious understanding of the fundamental mechanisms underlying the functions of the nervous system at different scales.

As an alternative, in recent years, there is a growing interest in the development of probabilistic models (Deco, Rolls and Romo, 2009; Harrison, David and Friston, 2005; Toyoizumi, Rad and Paninski, 2009; Cessac, 2011; Stevenson and Kording, 2011). This recent approach has the advantage of taking into account part of the available knowledge in neural system to construct parsimonious probabilistic models. This is an important advantage in comparison with the above described two approaches. However, until now many of this probabilistic oriented research suffers from two opposite limitations. Either they provide a rigorous mathematical description of some specific models, but without confronting them with experimental data set (see for instance Cessac, 2011). Or, they use some specific models to interpret experimental data, but without a systematic effort to study the mathematical properties of the models

(Toyoizumi et al., 2009; Harrison et al., 2005), which only analyzed through numerical simulations. The Center will overcome these limitations and build a bridge between the mathematical theory and statistical analysis of experimental data.

The probabilistic approach proposed by the Center has the potential of leading to significant advances, for three reasons: (i) the lessons learnt from previous failed attempts, (ii) the existence of massive databases, and (iii) the availability of new mathematical objects supported by a solid probabilistic theory. Members of the Center are, in fact, well known specialists, and even pioneers of the theory of these objects —context-tree models, new random graph categories, new model-selection procedures. Furthermore, the Center will be in conditions to generate large quantities of new experimental data to validate the approaches proposed. This combination of mathematical novelty and experimental design, together with the recognized scientific stature of the Center researchers should lead to significant contributions in the domain.

2.4 Scientific mission and the reasons for a Research, Innovation and Dissemination Center on Neuromathematics

The mission of the Center is to develop the new mathematics which is deemed necessary to account for a Theory of the Brain, accounting for the full experimental data gathered by neuroscience research. The long-term objective is to understand and explain complex neuroscientific phenomena, with focus on plasticity mechanisms underlying learning and memory, neurorehabilitation and adapted rewiring. This Neuromathematics is envisioned, at this time, as conjoining probability theory, combinatorics, statistics, and neuroscience. This requires the definition of a full new class of mathematical models to describe and explain in a parsimonious way the different scales of neural activity and the relationship between them. The construction of these models should occur together with the development of suitable statistical and computational methods, including model selection principles and results.

To fully achieve this mission, the Center will foster a new generation of neuromathematical researchers, uniquely equipped with mathematical, statistical and computational skills and access to extensive primary experimental data sets, enabled to propel a true breakthrough in this frontier of science. This will be achieved by articulated actions spanning the entire range of academic levels, from undergraduate and graduate students, through post-doc fellows, visiting scholars and resident faculty. The overarching goals of the Center are necessarily long-term and will require several years to fully blossom, since a novel and deep mathematical theory cannot be developed in a small amount of time.

Besides the long amount of time which is required to fully develop the NeuroMat scientific project, a new kind of organizational structure is needed, with no wall separating researchers from different scientific domains, different departments and even different universities. This is precisely the kind of structure provided by FAPESP proposal of Centers of Research, Innovation and Dissemination. This new NeuroMat center will be the ideal venue for a collaborative effort involving USP projects MaCLinC and NEAR together with Lucy Montoro Rehabilitation Center (São Paulo State), the Laboratory of Neurobiology II of the Biophysics Institute at UFRJ (Rio de Janeiro), the Brain Institute at UFRN (Natal) and CNRS’s Center of Cognitive Neuroscience (Lyon, France), together with an international team of top-level researchers coming from the different scientific domains involved in the NeuroMat project.

This effort will produce not only new scientific results in the frontier between mathematics and neuroscience, but will also train a new generation of researches able to do original research in this frontier. The project team has a long tradition on teamwork and training of productive, highly skilled human resources.

2.5 Vision of the Center

The center proposed here involves an interdisciplinary (and international) team of researchers and a selection of topics determined so as to guarantee two conditions: first, that the resulting theoretical work satisfy the four requirements listed above, and, second, that the research plan be realistic and reasonable given the NUMEC experience and the combined expertise of the team.

Understanding how animal behavior emerges from the interaction between neurons and between ensembles of neurons is one of the most important questions in modern neuroscience. It turns out that the mathematical models and tools developed by our team to study linguistic phenomena are natural candidates to approach this issue. Mathematically speaking, both linguistic and neuroscience models involve probability measures defined through graphs. In linguistics these are context trees retrieving linguistic dependencies. In neuroscience, models involve more complex graphs describing interacting neurons or clusters of neurons. The team's results on model selection — both for context tree models and for random fields supported by interaction graphs— are among the most advanced results available in this direction.

On the practical side, neuroscience theories cannot be developed without sufficient empirical validation. For this, the project has access to a large database, collected over a period of ten years by Sidarta Ribeiro, one of the founders of the International Institute of Neuroscience (IINN-ELS) in Natal, and a member of the team.

The proposed team undoubtedly measures up to the magnitude of the task. It is formed by first-level mathematicians working in probability, statistics, control and optimization, combinatorics and graph theory, well known mathematical physicists, computer scientists, engineers and a group of leading linguists. The members of the team belonging to the USP come from the Departments of Statistics and of Computer Science (IME-USP), the Department of General Physics (IF-USP), the Departments of Linguistics and of Classical and Vernacular Languages (FFLCH-USP) and the Department of Telecommunication Engineering and Control (EP-USP). The non-USP members include mathematicians, linguists and researchers in bioinformatics from the UFABC, UNICAMP and IMPA, a neuroscientist of the IINN-ELS in Natal and a large number of scientists from important foreign institutions (including the universities of Amiens, Buenos Aires, Cambridge, Cergy-Pontoise, Harvard, Princeton, Purdue, Roma La Sapienza and Utrecht, together with CNRS, Ecole Polytechnique Palaiseau and IBM).

2.6 Main scientific challenges and expected scientific discoveries

Until recently, the dominant paradigm in Neuroscience was to measure the activity of a single neuron or a brain area to correlate it with the animal behavior (Nicolelis and Ribeiro, 2006). The new technological progress through optical and chronic multi unit recording (Brown, Kaas and Mitra, 2004; Nicolelis and Ribeiro, 2006; Li et al., 2010; Takahashi et al., 2010) enables us to record the activity of thousands of neurons simultaneously for a period of days. Also, the progress of fMRI (functional magnetic resonance imaging) allows to record the global activity of whole brain for hours (Logothetis, 2007). The analysis of these data sets require the development of new statistical and computational paradigms. The probabilistic modeling of the brain activity is the natural approach to this problem, where the interactions between large numbers of neurons and brain regions can be described. These models must describe the fact that the interaction between neurons depends on the state of neuronal activation itself, and they are outside the scope of classical statistical mechanics. The analysis of these models requires new statistical tools beyond the existing multivariate methods. The mathematics necessary for this modeling, whose development is just beginning, is in the forefront of our research.

Neuromathematics The mathematical approach of the NeuroMat project is based on the premise that neural activity can be described as a probability measure on the space-time configurations of spike trains and neuronal interaction graphs. Such a measure can be called a neural state. Equivalently, a neural state is a non-stationary stochastic process, describing simultaneously the spike trains and the complex network of interactions between neurons. This stochastic approach provides economic explanations to well established experimental facts. For instance, this stochastic framework models in a natural way the observation that the same motor performance may activate different configurations of neurons every time it is repeated.

Previous mathematical modeling attempts in neuroscience involved Gibbsian (Newman, 1988) or Markovian descriptions that were shown to be inadequate (Friston et al., 2010; Truccolo et al., 2010; Cessac, 2011). Indeed, aging implies that the time between spikes is not exponentially distributed, and the firing time depends on the activity of neurons on a neighborhood that itself is a function of the collective configuration of the spike trains. This type of interaction does not correspond to a Gibbsian description. Furthermore, the connections between neurons define interaction graphs which experimentally are seen to be sparse and probably locally different from the tree graphs widely used in bioinformatics. New algorithms are needed to build and study the sparse locally non-tree interaction graphs.

The new approach proposed by the NeuroMat project involves continuous-time versions of chains with variable-length memory and variable-range interactions. These approaches are non-trivial extensions of both the Markov interacting particle systems introduced by Spitzer (1970) and of the variable length chains introduced by Rissanen (1983). They are inherently non-stationary in time and non-homogeneous in space. They represent a stochastic dynamics that change in response to external stimulia succession of samples produced by a random source - and also to internal stimuli by a procedure which is reminiscent of statistical model selection. In a different time scale, and making all the necessary adaptations, first language acquisition by a new born baby can also be described in this way.

Neural data set and modeling The analysis of neural data sets requires new statistical and computational schemes. On one hand, existing multivariate methods are largely insufficient and new statistical tools are needed to describe these readings. On the other hand, new mathematical models are needed to understand and interpret the observations. Probabilistic models describing interactions between large number of neurons and between brain regions offer a promising direction. Detailed data on brain activity are becoming available as a result of recent technological progress. For instance, optical and chronic multi-unit recording (Brown et al., 2004; Ikegaya et al., 2005; Nicolelis and Ribeiro, 2006; Takahashi et al., 2010) allows to record the activity of thousands of neurons simultaneously for a period of days. Also, fMRI (functional Magnetic Resonance Imaging) yields records of the global activity of the whole brain for hours (Logothetis, 2007).

In humans, the most common methods used to index neural state dynamics are based on electro-physiological [electroencephalograpy (EEG), magnetoencephalography (MEG), event related potentials (ERP) Transcranial Magnetic Stimulation (TMS)], as well as neuroimaging [fMRI, Magnetic Resonance (MRS), Near Infrared Sopectroscopy (NIRS), Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT)] measurements. While the temporal and spatial resolution of these methods are different, all of them have relatively low spatial resolution; they usually index activity at the network level. Because of their non-invasive nature, they are often associated with significant variability and low precision. Invasive methods to index neural organization in humans such as electrocorticography are also unable to index activity at neuronal level.

Overall, however, the limitations and strengths of these techniques are different, hence they should be used in a complementary fashion. For instance, fMRI is a suitable complement for MEG and EEG. The former provides relatively reasonable spatial resolution of head and brain anatomy, while the latter provide excellent temporal resolution. Most studies, however, rely on a single technique or in separate interpretations of results whenever multiple techniques are used. NeuroMat aims to develop mathematical methods to extract combined information provided by these methods when used simultaneously.

Mathematics, plasticity and neurorehabilitation One of the most influential concepts that emerged in the 20th century in the domain of neuroscience refers to the brain's capacity of constant remodeling. It was long believed that the synaptic networks, and consequently, the functional organization of the brain, were hard wired from birth and could not change during adult life. This view was first challenged by Donald Hebb (1949) who suggested that synapses were continuously remodeled by experience.

Contemporary research has shown that throughout an individual's life, dendrites and spines branches and proliferates, novel synapses are formed, some of them degenerate, and the efficacy of synaptic contacts is modulated within a complex network of connections (Buonomano and Merzenich, 1998; Nudo, 2003). The term plasticity was first coined to refer to the brain's capacity for such changes (review in Kaas, 1983), occurring not only during development but also as a consequence of learning and memory, in response to disease, or as a response to therapy (Cramer et al., 2011). Such plasticity can be viewed as adaptive when associated with improvement of functions (Cohen et al., 1997) or as maladaptive when associated with negative consequences such as loss of function or increased injury (Nudo, 2006). Therefore, mathematical models are needed also to encompass dynamic alterations associated with plasticity that may vary according to the post-injury phase.

Post-injury plasticity has not only been extensively documented at the molecular, synaptic, cellular, network, and systems levels in experimental animals, but many of these events have been correlated with alterations in cortical function with the use of various neuroimaging and stimulation techniques in humans. The state of art in the field of post-injury plasticity is still at a phenomenological stage (Nudo, 2003). Furthermore, compelling evidence from large studies involving clinical trials to reveal clinically relevant plasticity is still needed. From the clinical point of view, the fundamental need in harnessing neuroplasticity is to reliably demonstrate behavioral improvements in human populations through the validation of prognostic indicators and the identification markers of efficacy to assist clinical trials (Cramer et al., 2011). Advancements in this direction will also guide development of novel interventions.

Neurological damage, and stroke in particular, is one of the leading causes for long term disability worldwide. There is growing interest in the role that central nervous system reorganization plays in recovery of function. Understanding how these changes are related to functional recovery will facilitate the development of novel therapeutic techniques that are based on neurobiological principles and that are designed to minimize impairments in appropriately targeted patients suffering from stroke (Ward, 2005).

The comparison between normal and altered brain states has been limited by the poor information about the connectivity between neurons and brain areas. It must be made on the basis of the measured neuronal activity patterns of individual neurons and/or the whole network (Park and Terman, 2010). The probabilistic models proposed above are general enough to provide a sound mathematical framework for the required comparison. Its statistical analysis, however, is complicated by their non-Markovian character and the fact that the interaction between neurons depends on the activity of the neurons themselves. This statistical analysis must be accompanied by extensive processing of experimental data. This combination of mathematical modeling with statistical and experimental validation is precisely the type of study to which the present proposal is geared.

Identification of altered states is only the first step. Functional recovery must follow. Mathematical modeling is increasingly being used both in animals and humans to predict clinical outcomes (Ring et al., 1999) and to develop novel therapeutic tools. Neuronal activity of groups of neurons may help to identify patients who will respond to rehabilitation and have functional recovery potential. Therefore, the appropriate treatment of this mathematical information will be of great importance in clinical practice. The sophisticated probabilistic models proposed in this project should lead to better predictions on the functional recovery and learning abilities in stroke patients. To validate these predictions the project will build a large database using data from patients from the Net of Rehabilitation Hospitals of the Lucy Montoro Rehabilitation Institute, and a mobile unit especially designed to collect data from remote sites. Predictions derived from the mathematical models will be used to standardize rehabilitation treatment for stroke patients, to identify predictors of response and likelihood of response, and also to develop novel interventions to enhance functional recovery after stroke.

Memory A number of studies indicate that, during sleep, important neurophysiological process related to the consolidation and reorganization of memory take place. Since 1989, several groups have suggested that the reactivation of patterns of neural activity observed in awakeness during the slow wave (SW) and rapid-eye-movement (REM) sleeps (Ribeiro et al., 2004; Hirase et al., 2001; Dragoi and Tonegawa, 2011) can be interpreted as evidence for the reproduction of the information acquired during awakeness (Ribeiro and Nicolelis, 2004).

To verify this conjecture, it is necessary to compare the neural activity during awakeness, SW and REM. The main difficulty is that only part of the activity is observed and no direct information about the connectivity between neurons is usually available. To make the task even more difficult, the interaction between neurons could depend on the activity of neurons itself. To overcome these difficulties, a first step was given by Galves et al. (2010) and Lerasle and Takahashi (2011). In these works it is assumed that the interactions do not depend on the activity of neurons, which simplifies the analysis.

The next step will be to allow the interactions to depend on the state of activity, generalizing the chains of variable length introduced by Rissanen (1983). For this, new mathematical and statistical theories of stochastic systems with variable length interactions must be developed. Also, these problems involve hard combinatorial and computation problems.

Besides the mathematical, statistical, and computational development, an adequate structure for neural data analysis will be necessary to apply these methods in practice. For this, a new Data Analysis Laboratory will be implemented, which will considerably enhance the quality and quantity of statistical analysis of scientific data developed by the team.

As a starting point, electrophysiological recordings from the cerebral cortex and hippocampus of adult rats will be used. The animals were recorded for several hours, such that the complete awake-sleep cycles were observed. The recording corresponds to three different conditions: before, during, and after the tactile experience with four new objects. Published results using this data set indicate that the average spiking rate is enhanced during sleep after the novel tactile experience (Ribeiro and Nicolelis, 2004). The statistical methods developed by NUMEC will be used to elucidate the dynamics of neuronal interaction during different awake-sleep states in different conditions.

2.7 Specific Research Directions

To achieve significative progress on the scientific challenges listed above it is essential to develop a realistic course of action that takes full advantage of the two strong points of the proposed centre: the original mathematical approach adopted and the unique combination of domains of expertise of its members. To this end, the Center proposes to group the theoretical research along two main categories to be developed simultaneously.

Modeling the dynamics of neural activity Neurons, and more generally neural structures and activities are characterized by the large number of its components and the non-trivial dynamic interaction between them (Braitenberg and Schüz, 1998): at each level of activity (neurons, cortical columns, brain areas) the graphs of interactions change in time (Eguiluz et al., 1995). These complex characteristics are revealed by in neural data sets at all scales, from multi-unit registers of a hundred of neurons, to EEGs with hundreds of channels and to fMRI data with thousands of voxels, each channel or voxel reflecting the activity of millions of neurons and finally to behavioral data.

A new class of stochastic processes –with values on a combined space of neural activities and interactions– must be developed to describe these phenomena and the resulting data structure. These processes provide the mathematical bridge between neural activity at different levels, from local to global, by relating the time evolution of neuron configurations to global probability distributions.

The new class of stochastic processes considered in this project involve large numbers of interacting point processes with interaction graphs varying in time and in space. A fixed finite system of interacting point processes has been used to model neural activity, for instance by Brillinger (1975) in his modelling of two neurons of a sea slug by two interacting point processes. The multiscale character of neural phenomena, however, requires the use of large systems linked by interactions that evolve in time and depend on the history of the system.

This dependence on histories can be seen already at the level of single neurons. Indeed, observations show that the probability that each neuron fires at a fixed time depends on the time-integrated synaptic input from interacting neurons. Firing happens when this integrated input exceeds a certain threshold within some time period. Hence the firing probability depends, in a variable manner, on the past and the neighboring neurons (see, e.g., Cessac, 2011).

The models proposed here are natural generalizations of the chains with variable-length memory (see, e.g., Rissanen, 1983; Bühlmann and Wyner, 1999; Galves and Löcherbach, 2008). Their properties put them outside the framework of classical statistical physics and the usual theory of stochastic processes. New mathematics is needed. The members of the center, however, have the required expertise to develop these new theories. Indeed, the team is formed by many leading specialists in non-Markovian processes and non-Gibbsian measures, including variable-length processes, and fields (Bressaud, Fernández and Galves, 1999; Comets, Fernández and Ferrari, 2002; Galves and Leonardi, 2008; Galves, Löcherbach and Orlandi, 2010; Galves et al., 2012; Garivier and Leonardi, 2011; Gallo, 2011; Collet, Galves and Leonardi, 2008;) and Gibbsian and non-Gibbsian formalisms (van Enter, Fernández and Sokal, 1993; Fernández and Maillard, 2005).

As a complementary point of view, these processes can be thought as stochastic evolutions of graphs. Hence, its study also pertains to the theory of random graph models. The central issue is to definine probability measures on the space of finite but large graphs and to consider their time evolutions. The current literature on brain graphs (Bullmore and Bassett, 2011) focuses on important but "low dimensional features" (or projections) of the graphs, such as degree distribution, clustering coefficient, average distance between pairs of vertices, etc. A more sophisticated approach is required to access the high-dimensional aspects of neural systems. This approach can be built from promising developments in graph theory, such as the powerful "coarse-grained" representations of graphs —Szemerédi's regularity lemma (Sze-merédi, 1976)— or the continuous representations such as the "limit object" known as graphons (see, e.g., Lovász, 2009).

Graphons naturally lead to the so-called consistent local random graph models (they are in fact equivalent to them; see the Section 6.5.1 of Lovász, 2009), which in turns is the starting point for the definition of inhomogeneous random graphs (Bollobás et al., 2007). These graphs encompass the most significant models of scale-free random graphs and are suitable to rigorous mathematical analysis. Furthermore, Bollobás et al. (2011), generalized this model to obtain models exhibiting high clustering, a feature of interest for neural datasets. The Center intends to use these models —as well as those proposed in Bollobás et al. (2007) to develop new models leading to efficient statistical and computational tools and to wider model selection principles.

Inferring functional interaction between neural structures While neural activity can be directly observed, interactions between neural structures can only be inferred from data. Traditionally, this has been done using descriptive statistics methods like linear correlation, which give little insight on the mechanism underlying the dynamics of the neural activity (Brown et al., 2004). A different, deeper maximum likelihood model selection point of view was introduced by Brillinger (1988). More recently, models developed in statistical mechanics, e.g., the Ising model, have been used to infer the system of neural interactions (Schneidman et al., 2006), with the caveat that the results are difficult to interpret as the Ising model has no resemblance with known neural processes. Added to these difficulties, there is little rigorous statistical theory that justify the respective statistical and computational procedures. One of the goals of the project is to develop the statistical theory needed to analyze samples generated by large systems with interactions of variable range in time and space.

This issue has many aspects to be considered, some of which have started being addressed by members of the proposed Center. A prioritary issue is how to infer global states from local observations. Indeed, in most cases the experimental data set represents only a sample of a tiny portion of the neural system. —even modern multi-unit recording can register at most hundreds of neurons, not necessarily synaptically connected with each other. Given this partial observation, it is not clear how to interpret results obtained from statistical methods designed to recover the interaction neighborhoods between neurons (for example Schneidman et al., 2006). In Galves et al. (2010), it is shown that a probabilistic method called coupling gives a natural way to answer this question. More specifically, the results of Galves (2010) show that when only part of the system is observed, and assuming that the observed realization comes from an Ising model, the algorithm presented by Schneidman et al. (2006) recoversthe interaction neighborhood up to an error which can be explicitly bounded.

A second issue is how to infer functional interactions between components. In a toy model of a neural system, Lerasle and Takahashi (2011) introduced an oracle approach for selecting optimal interaction neighborhoods. Oracle techniques are in the forefront of current model selection theory and have a sound mathematical justification based on recent results on the theory of concentration of measures (Massart, 2007). Lerasle and Takahashi (2011) introduced a model selection criterion and proved a corresponding oracle inequality. They generlized and sharpened their work in Lerasle and Takahashi (2012).

From a practical point of view, an inference problem can only be considered to be effectively solved if the resulting estimator is computationally efficient as well as theoretically sound. In the onedimensional case, efficient estimators and algorithms are known for inferring past dependence in variable length processes (Willems et al., 1995; Csiszár and Talata, 2006). But the generalization of these algorithms to higher dimensions seems to be an elusive problem (Csiszár and Talata, 2006). Interestingly, for general interactions, there is a trade off between theoretical generality and the computational complexity of the neighborhood inference procedure. Generality comes with an increase of computational demands. The control of this tradeoff is an important practical issue.

Surprisingly, a large body of recent work in a different field —linear regression problems— yielded efficient sparse estimators for data set with a large number of parameters. Examples include the LASSO (Tibshirani, 1994; Efron et al., 2003) and the Dantzig selector (Candes and Tao, 2007). These linear regression ideas will be explored by NeuroMat members to obtain better algorighms for the neighborhood selection problem.

Summing up, the research projects will focus in the following problems of computational statistics:

1. The use of convex programming in statistical estimation, in the same spirit as the LASSO and the Dantzig selector, as well as other known efficient techniques;
2. The study of the feasibility of basing statistical estimation on approximation algorithms, whenever the complexity of exact estimation is unavoidably high;
3. The determination of the power and limitations of fast and simple algorithms (such as greedy algorithms).

Progresses in these directions will require a cooperative work of computer scientists, mathematicians and statisticians. The development of efficient estimators is a long process involving the balanced interplay between statistics and computer science. The NeuroMat team has the necessary blend of expertise needed s to face this challenging issue.

2.8 Case studies

The two research directions just described will encompass a number of specialised projects focused on issues that are pivotal for the program of the Center. Each project will be lead by an experienced mathematician and involve a combined team of neuroscientists and clinicians. In addition, and in consistency with the formative objectives of the Center, each of these focalised projects will involve advanced students and young researchers. For the sake of concreteness, we present a more detailed description of one of these projects, followed by a list of other projects that are already being developed in anticipation to the creation of the Center.

Modeling memory acquisition using systems of stochastic chains with memory of variable length The project enquires about the mechanisms underlying the acquisition and transformation of memories over time, with a focus on the cognitive role of sleep. This issue is largely unresolved, despite important recent research. In particular, it has been conjectured that sleep promotes the corticalization of hippocampus-dependent memories (Ribeiro and Nicolelis, 2004).

To address this problem, Sidarta Ribeiro and collaborators used multi-electrode micro-wire arrays to perform chronic electrophysiological recordings of single and multi-neuron signals before, during and after the acquisition of novel memories. The targeted brain areas comprise the hippocampus (HP), the primary somatosensory cortex

(S1), and the primary visual cortex (V1), chosen because of their direct involvement with tactile (Simons and Woolsey, 1979), spatial (O'Keefe, 1979) and visual (Hubel and Wiesel, 1959) processing, respectively. All three areas show persistent changes in neuronal activity during post-experience sleep (Ji and Wilson, 2007; Pavlides and Winson, 1989; Ribeiro et al., 2004, Vasconcelos et al. 2011), and respond to novel stimulation with robust biochemical changes related to memory processing (Wallace et al., 1995; Grimm and Tischmeyer, 1997; Ramirez-Amaya et al., 2005; Ribeiro et al., 2007).

The experimental arrangement consists in exposing rats to novel objects for a short time in order to induce the construction of new memories. The recordings are subsequently processed to determine the evolution of the interaction network across the sleep-wake cycle and to seek for memory traces in the forebrain. Mathematically, the treatment of the recording amounts to a statistical model selection problem: A model must be selected to describe the sample during the periods in which a rat is exposed to a novel object. The conjecture is that the selected model is a " signature" of the reaction of the animal to the new object. The question is whether the same model (the same "signature") can be found during the sleep cycle.

Model selection involves two equally important steps: (i) the choice of an appropriate class of candidate models, and (ii) the choice of a procedure to select a member of this class. As discussed above, the Center proposes stochastic chains with memory of variable length as the general class of models apt to describe neural data. The second step, namely the model selection procedure within this class, has been addressed in a number of papers, starting with Rissanen (1983) who introduced the so-called Algorithm Context. An incomplete list of subsequent improvements includes Bühlmann and Wyner (1999), Galves and Leonardi (2008) (see also Galves and Löcherbach, 2008 for a survey). A different approach was proposed by Csiszár and Talata (2006) who showed that context trees can be consistently estimated in linear time using the Bayesian Information Criterion (BIC).

Both the Algorithm Context and the BIC procedures require the specification of a constant modulating, repectively, the pruning threshold for the Algorithm Context, and the penalization for the BIC. These constants have no effect on the consistency of the algorithm, but it becomes very important for finite —even very large— samples. Recently Galves et al. (2012) introduced the Smallest Maximizer Criterion which is a constant free procedure that selects a context tree model, given a finite data sample.

A further important issue in the analysis of systems of spike trains is the determination of the alphabet needed to describe the sample configurations. Researchers of the Center have also a novel idea for this issue: For each novel stimulus select a family of models respectively adapted to the system of spike trains produced by different subsets of neurons. This approach open the tantalizing possibility of identifying interactions between neurons through the different context-tree models selected for different subsets of neurons.

This line of investigation is presently being developed by a Research Cell of the NeuroMat project, formed by the mathematicians A. Galves and J. Garcia, the neuroscientists S. Ribeiro and N. Vasconcelos and a statistics PhD student K. Yaginuma.

Further projects The following is a list of projects already started by members of the proposed Center. Two features are noteworthy: Each cell involves scientists of complementary disciplines, and each of the projects is based on experimental data collected by participants of the project.

Inferring brain interaction graphs using electroencephalographic recording with applications to the follow up of stroke patients. Research cell: C. Vargas (neuroscience), D. Fraiman (statistical physics), A. Galves (mathematics), plus a postdoc to be appointed. Data collected by Claudia Vargas.

Kolmogorov-Smirnov projective test for fMRI data. Research cell: G. Xavier (neuroscience), A. Iambartsev (mathematics), J. Garcia (mathematics). Data collected by G. Xavier.

Using splines to characterise fMRI data. Research cell: N. Garcia (mathematics), G. Xavier (neuroscience). Data collected by G. Xavier.

Non-parametric tests of hypotheses for neural networks. Research cell: R. Freiman (mathematics), F. Leonardi (mathematics), F Fregni (neuro clinician). Data collected by F. Fregni.

Bayesian algorithms to assist clinical diagnosis in AVC patients. Research cell: V. Gonzalez-Lopez (mathematics), J. Garcia (mathematics), L. Rizzo Batistella, (neuro clinician). Data from databases of the Lucy Montoro rehabilitation center.

The ongoing research. Updated reports on the subprojects currently under development by the Reseach Cells of the NeuroMat team will be periodicalymade available at our website: http://neuromat.numec.prp.usp.br

2.9 Role of technology transfer and dissemination activites

The whole of the project is organized as an interplay between theoretical advances and technology transfer. There is a two-way communication between both activities. On the one hand, the theoretical research relies on data provided by rehabilitation institutions and is oriented by clinical needs. On the other direction, theoretical research is expected to assist on diagnosis and recovery evaluation and give new insights to clinicians designing rehabilitation techniques.

Regarding dissemination activities, a research enterprise of the scope of NeuroMat can not survive without public awareness. This awareness is needed to justify the required support in resources and to ensure its perpetuation over a period of several years. Dissemination is, at the same time, crucial to attract the steady flow of young researchers needed to keep the Center alive with people and ideas. The Center has designed, therefore, an intense program of activities to bridge the gap between scientific production and knowledge dissemination.

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