RESEARCH STATEMENT

I obtained my Ph.D. degree in 2005 at the State University of New York at Stony Brook, with a dissertation in real dynamics, under the supervision of Distinguished Professor John Milnor. My areas of mathematical interest include ergodic theory, topological dynamics and kneading theory. My work as a graduate student in mathematics was focused on the question of how dynamic complexity of a discrete system evolves under deformations. My Ph.D. thesis addressed topological properties of the entropy within a two-parameter family of polynomials, as well as the computational question of whether there is an optimal algorithm to calculate the entropy within this space. Since graduation, my research has combined my background in dynamical systems and systems complexity with a sustained commitment to biological modeling.

Passed and current research

During postdoctoral years, the target of my research has contoured more clearly around the modeling and mathematical analysis of nonlinear neural networks, together with their applications to a large variety of fields. My interest focuses on understanding the organization and function of the brain in particular, and on quantifying the differences between a healthy system, operating in an optimal range, and the disrupted dynamics responsible for pathologies. At the center of my research is the question of how the hardwired *structure* of the network (graph), in conjunction with the *coupled dynamics* of its nodes, affect the *function of the system* (e.g., in the context of optimal information storage, or node-to-node transmission along time). One of the exciting aspects of this work is using mathematical (theoretical and numerical methods) to create a quantitative framework, and use it to verify hypotheses (or suggest theoretical alternatives) about organization and function of neural circuits. These hypotheses are testable empirically, and can be used to build theories about brain processes, cognition and behavior.

My work addresses this broad question in many forms, with a wide combination of tools, and (sometimes simultaneously) at multiple spatio-temporal scales (from that of a single cell, to neural network, to the macroscopic scale of brain regions, compatible with imaging studies and behavior). My recent work has been addressing all of these scales, through a combination of mathematical, numerical, control engineering and clinical approaches, and with the help of collaborations in neurophysiology, imaging, behavioral psychology and psychiatry. The long-term aim is to generate a whole comprehensive, yet mathematically tractable theory, allowing analysis, computation and experiment to interact and capture the complex nature of the human brain. The overarching clinical goal of this type of research is to use modeling towards developing more reliable clinical assessment methods, customized to each individual's particular neurophysiology. Beyond this, similar tools can be used to analyze many seemingly unrelated complex systems. Below are outlined the recent projects that best illustrate the flavor of this research.

My recent and current work with clinical data has been on neuroimaging and heart rate time series, and consists of combining standard statistical measures of variability with more network-oriented measures of regularity in a system. These are aimed to capture the nonlinear feedback interactions that are broken in emotional dysregulation such as anxiety, depression, bipolar disorder or schizophrenia. Most of this work has been conducted in collaboration with Lilianne Mujica-Parodi and the Laboratory for Computational Neurodiagnosis (LCN) at Stony Brook University, as well as the Martinos Center for Biomedical Imaging at Harvard. We are using reconstructive, bottom-up methods (time-delay embedding), as well as top-down methods (computation of dynamic invariants) to quantify the system's complexity, working in the phase space (approximate entropy, Lyapunov spectrum) or in the frequency domain (power spectra scale invariance, PSSI). Using PSSI, we were able to localize the neural dysregulation signature of different pathologies to particular brain areas. For example, we found patients with schizophrenia to show a power spectru slopes significantly closer to 0 (hence more chaotic signals) than healthy controls in Brodmann Area 10 of the prefrontal cortex, while high anxiety subjects had flatter amygdala spectra than low anxiety subjects.

Simultaneously, I have been using concepts from dynamical systems to understand mechanisms like learning and

memory formation. In joint work with the Adams lab, we have been investigating the effects of synaptic cross-talk on the accuracy of Hebbian learning, in particular in the context of binocular separation of inputs. While this views synaptic plasticity as the strengthening or weakening of individual synaptic weights, my newest work aims to incorporate the geometric configuration of the network. Recent theories suggest that realistic complex behavior, comparable to neural behavior, cannot be obtained from either a structure too globally rigid, or from only locally-based connections. We are using results from random matrix and graph theory to understand the combination of features (robust vs. random, long vs. short-range, hub-like vs. uniform) that allows enough dynamic flexibility, yet renders the system sufficient stability for convergence during a cognitive process such as learning. To assess the changes in network dynamics produced by perturbations in the underlying graph, we are using phase-plane plots and bifurcation diagrams. Some of the network modeling results have already been used in conjunction with fMRI data, to understand how connectivity affects critical dynamics in the neural circuit that regulates emotion. When unifying the fRMI results from two studies run by LCN on subjects covering the entire anxiety range, our modeling results suggested a testable framework for interpreting empirical data.

This year, I have been additionally working on obtaining funding for two new collaborative endeavors, aimed to explore applications of nonlinear tools to more clinical contexts. My recent work with the Kent Kiehl group, at the Mind Research Center at the University of New Mexico, is addressing neural architecture and dynamics in criminally psychopathic behavior. A second project, expanding my collaboration with LCN, is focused on understanding the impact of node-to-node network "lesions" to the localization and dynamics of epileptic seizures.

Proposed research

The proposed course of research over the next few years consists in constructing a multi-scale model of complex dynamic architecture in the neural networks governing emotion. The brain circuits regulating emotion are an ideal candidate for systems modeling, since they have been relatively well-mapped in basic rodent research. The model will therefore integrate basic and human aspects, with the general aim of providing a theoretical bridge between outward effects and the underlying biophysics, while generating predictions that can be further tested empirically.

At the macroscopic scale, the model should be compatible and validated with human imaging data, while at the microscopic scale, it will be compatible with electrode and optometric recordings both in rodents and in humans. Existing data obtained with various imaging techniques from subjects with emotional dysregulations (publicly available functional MRI, EEG, near infrared spectroscopy, diffusion tensor imaging data sets) will be used in conjunction with the theoretical model, to estimate the dynamic range for each subject. The predicted and empirical estimates obtained for these dynamic invariants can thus be directly compared. We will use a combination of analytical and computational tools to study the effects of coupling parameters and geometry on the system's dynamics. Further iterations of the model are to incorporate biophysical details of the prefronal-limbic network (using, at the neural/synaptic spatio-temporal scale, information on connectivity and dynamics from empirical rodent models). Once the model is successfully tuned at both scales, it can be further used to make clinical classifications and predictions of prognoses, in human subjects with a spectrum of emotional dysregulations. Model-based classifications and predictions could be compared with the subjects' diagnoses and prognoses made in the clinician's office.

While there is growing interest in studying the temporal architecture of the brain, such research has been so far typically either primarily theoretical or primarily empirical. Bridging the two extremes is as difficult as it is necessary, since the ideal approach requires training from pure mathematics and computational neuroscience to neurophysiology and engineering. The PI has invested considerable effort in building this background, as well as a wide network of collaborations from both theoretical and clinical ends. The resulting research represents a marked departure from the approaches currently used, in that: (1) it includes novel and specifically-optimized network-based quantitative methods in conjunction with both neuroimaging and theoretical modeling; (2) it is explicitly translational, including in the model formal components from both animal and human studies; and (3) the techniques have the potential to be generalized to other neural circuits, and further to other conditions of network dysregulation.

Conditions of emotional dysregulation — such as anxiety, bipolar disorder, major depression or schizophrenia —

are severe mental illnesses with a devastating impact on personal and social functioning, affecting billions of people worldwide. Emotional disorders continue to show a surprising resilience to establishing biomarkers via methods such as genetic sequencing, electrode recordings, and structural or functional brain studies. Their diagnostic criteria are based upon statistically common behavioral symptoms, which do not necessarily reflect the underpinnings of the illness. Outward signs of emotional disorders are complex and widespread, making symptom-based clinical decisions unreliable, especially since these symptoms rely upon patient compliance for self-reported behavior and are often compatible with multiple diagnoses. In addition, decisions cannot be made until symptoms develop, which may already be too late for optimal intervention. Despite pharmacological progress, the field has thus far failed to establish clear mechanisms defining and separating emotional disorders. Even new medical treatments may address only the effects rather than the cause of the illness. Therefore, a quantitative assessment system would be extremely desirable, allowing clinical decisions based on clear neurobiological mechanisms, rather than on their outward manifestations. The overarching goal of this research is the development of a neurobiologically-based diagnostic instrument ("brain profiling") that could provide clinicians with a look-up table to map out diagnosis, severity, or even risk before symptom onset, optimizing prognosis and treatment efficiency.

IST mentoring

I feel that the IST fellowship is very appropriate for the current stage of my career. Over the past eight years since obtaining my Ph.D., my postdoctoral training has been quite unusual. I have been taking temporary academic positions with heavy loads of mathematics teaching, in order to remain in Boulder, CO, with my family. While this extensive period allowed me to consolidate the interdisciplinary aspects of my research, it has also made it difficult to start on an independent research path. I feel that my level of experience transcends that of a junior researcher, and is appropriate for starting on the research plan described above. From the description, the IST fellowship seems to provide the ideal combination of mentored, collaborative and independent work, which is one of the reasons I am applying. In addition, the geographical location would allow me to be closer to my parents, and together with my spouse (who will be simultaneously visiting the Mathematics Department in Vienna).

I would be looking forward to work with a few groups at IST, with very exciting systems and neuroscience research, relevant to my own. Overall, the work performed by the ***Tkačik group*** overlaps significantly with my desired approaches to study information processing and adaptability of biological networks. My interest resides both in gaining more experience with using statistical physics methods to study system order and noise, as well as in learning about new applications of such methods (e.g., to understanding collective behavior in networks of neurons). I am also highly interested in ***Hippenmeyer group***'s explorations of the connections between cortical cytoarchitecture and behavior, and in the work on hippocampal interactions performed by the ***Csicsvari group***. These represent very exciting basic neuroscience counterparts of my own interests in understanding brain temporal architecture in humans, and its connections with emotion, cognition and behavior. Finally, because of my work on synaptic plasticity and cross-talk, I would be interested to better understand the empirical work from the ***Jonas group*** on synaptic signaling in the hippocampus (especially since parvalbumin-containing interneurons have been related to abnormal oscillatory patterns in rodent models of schizophrenia).