

Yale University

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Brown University
38 George Street
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April 23, 2012

Dear Committee Members,

I am writing this letter to apply for the position of Assistant Professor in Computational Neuroscience at Brown University.

The goal of my research is to uncover the principles of signal processing in neural circuits, with a special interest in the neural circuit mechanisms of cognitive functions. My long-term goal is to explain the behavior observed in mental and neurodegenerative diseases in terms of failures of neural circuits. To achieve this goal, I study the dynamics of neural activity in subjects engaged in cognitive tasks. It has been increasingly appreciated that the dynamics of neural activity plays a crucial role in signal processing and cognitive functions. More broadly, I am interested in applying state of the art statistical and modeling techniques to biological data, and contribute to the increasing number of groundbreaking discoveries in quantitative biology. My approach includes a combination of analysis and modeling of neural circuits, using the methods of Statistical Inference, Theoretical Physics and Machine Learning. Please see my research statement for further details.

I have presented my work at international scientific workshops, conferences and invited talks. My research is published in peer-reviewed scientific journals (e.g., *Nature Neuroscience*, *Proceedings of the National Academy of Sciences USA*, *Cerebral Cortex*, *Journal of the Royal Statistical Society*), and my articles are co-authored with individuals from six different research groups. I have received international research awards and fellowships (Persico Prize, INFN fellowship, Swartz Fellowship) and I have served as ad hoc reviewer for various international scientific journals (e.g. *Cerebral Cortex*, *PLoS Computational Biology*, *PLoS ONE*). Please see my curriculum vitae for further details. In addition to my scientific output, I have excellent experience as a classroom instructor and supervisor for research projects. I have mentored four students during their internship or doctoral theses, and I have served as a teaching assistant in five courses (Neural Networks, Physics, Computational Physics, Multivariate Analysis and Extreme Value Theory). Please see my teaching statement for further details.

During my academic career, I have developed, analyzed and simulated computational models of neural circuits, and collaborated with experimental laboratories in testing those models. Trained in Theoretical Physics, during my Ph.D. I studied the neural circuit mechanisms of learning and memory. Following my doctorate, I realized that my background was not sufficient for pursuing a career in Computational Biology, and I needed additional skills in both Statistics and Biology. First, I participated in a two-year project focused on the methods for analyzing large datasets; I developed novel statistical techniques for multivariate analysis and applied them to the study of gene expression arrays. Second, I spent three years at the Yale Medical School, studying how primate cortical neurons integrate stimuli. The interdisciplinary environment at the Yale Medical School has greatly increased my knowledge in Biology and improved my communication skills.

My research focus seems an excellent and non-redundant fit with areas of strength at Brown University. I seek colleagues having complementary strengths and broad interests, Brown seems to be an exceptionally conducive and interdisciplinary environment and I see great potential for productive mutual exchange. My research is at the intersection of Computational Biology and Theoretical Physics, and has the potential to tie areas together. I see great potential for productive mutual exchange with faculties in Neuroscience, Cognitive and Computer Science.

Please find enclosed my curriculum vitae (including a list of publications and references), research statement and teaching statement. Please contact me if you have questions or if I can provide additional materials that would be helpful to the search committee. I am very excited about the possibilities for conversation and productive collaboration with the current faculty at Brown University. I appreciate your consideration of my application and look forward to hearing from you.

Sincerely,

A handwritten signature in black ink, appearing to read 'Alberto Bernacchia', written in a cursive style.

Alberto Bernacchia

Alberto Bernacchia

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EDUCATION

Yale University

Postdoctoral Associate

New Haven, CT

2008-present

La Sapienza Universita

Postdoctoral Associate

Rome, Italy

2006-2008

La Sapienza Universita

PhD, Neuroscience

Rome, Italy

2002-2006

Ecole de Physique des Houches

Methods and models in Neurophysics

Les Houches, France

2003

La Sapienza Universita

Laurea, *magna cum laude*, Physics

Rome, Italy

2001

GRANTS AND AWARDS

Swartz fellowship

Swartz Foundation

2008

INFM fellowship

Italian Institute of Condensed Matter

2002-2005

Enrico Persico prize

Accademia dei Lincei (rank 1st among student of Physics in Rome)

1998

RESEARCH EXPERIENCE

Yale University

Postdoctoral Associate; Advisor: Xiao-Jing Wang

New Haven, CT

2008-present

- Neural circuit modeling of temporal integration in decision-making
- Theoretical studies of neural correlations in disordered networks.

Consiglio Nazionale delle Ricerche

Research Assistant; Advisor: Paola Bertolazzi

Rome, Italy

2007

- Analysis of gene expression data in DNA microarrays.

Centre National de la Recherche Scientifique

Visiting Researcher; Advisor: Philippe Naveau

Saclay, France

2006

- Multivariate theory for the analysis of extreme events.

La Sapienza Universita

Postdoctoral Associate; Advisor: Alfonso Sutera

Rome, Italy

2006-2008

- Self-consistent theory of density estimation.

Hebrew University

Visiting Student; Supervisor: Volodya Yakovlev

Jerusalem, Israel

2004

- Spike sorting of neuronal *in vivo* recordings in behaving monkeys

La Sapienza Universita

Graduate Student; Supervisor: Daniel J Amit

Rome, Italy

2002-2006

- Synaptic theory of attractor dynamics.
- Neural network (attractor) models of working memory.

TEACHING EXPERIENCE

Yale University	New Haven, CT
Guest Lecturer, Computational Neuroscience	2012
La Sapienza Universita	Rome, Italy
Guest Lecturer, Multivariate Analysis (Graduate School)	2007
Guest Lecturer, Extreme Value Theory (Graduate School)	2007
Teaching Assistant, Computational Physics (1st year undergrad.)	2006
Teaching Assistant, Physics (1st year undergrad.)	2003-2004
Teaching Assistant, Neural Networks (4th year undergrad.)	2003-2004

INVITED TALKS

"Stretching of memory in strategic decision making", Center for Neural Science, **New York University**, New York, NY, March 2012

"A statistical theory of neural memory traces", Center for Theoretical Neuroscience, **Columbia University**, New York, NY, June 2011

"A statistical theory of neural memory traces", Department of Physics, **La Sapienza University**, Rome, May 2011

"A reservoir of time constants for reward memory in the anterior cingulate cortex", **Gordon Conference: Neurobiology of Cognition**, Waterville Valley, NH, August 2010

"Learning and memory of discrete and continuous sets of stimuli", Department of Physics, **La Sapienza University**, Rome, June 2008

"Dynamics of attractors in a plastic neural network model driven by morphed stimuli", Center for Theoretical Neuroscience, **Columbia University**, New York, NY, April 2007

"A neural network model for attractor dynamics and visual response to morphed stimuli", **International School for Advanced Studies**, Sector of Cognitive Neuroscience, Trieste, February 2007

"Effects of spatiotemporally correlated stimuli over plasticity and retrieval in a binary neural network", Laboratory of Neurophysics and Physiology, **Universite Rene Descartes**, Paris, October 2006

"The interplay between learning and memory in a highly correlated environment: a solvable model". **Max Planck Institute** for dynamics and selforganization, Goettingen, September 2005

CONFERENCE PROCEEDINGS

Bernacchia A, Wang XJ (2012) Stretching of memory in strategic decision making *Computational and Systems Neuroscience (Cosyne) 2012*.

Bernacchia A, Seo H, Lee D, Wang XJ (2010) Dissociating the timescales of short-term memory in neurons of the primate neocortex. *Program No. 102.12/LLL7. 2010 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience*. Online.

Bernacchia A, Seo H, Lee D, Wang XJ (2010) When to recall a memory? Epoch dependent memory trace with a power law of timescales in ACC neurons. *Front. Neurosci. Conference Abstract: Computational and Systems Neuroscience* doi: 10.3389/conf.fnins.2010.03.00026

Bernacchia A, Wang XJ (2009) Learning expected rewards in a volatile environment: A random network model endowed with a reservoir of timescales. *Program No. 102.5/FF77. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience*. Online.

Bernacchia A, Wang XJ (2009) Neural correlations in a heterogeneous network model dominated by recurrent inhibition. *Frontiers in Systems Neuroscience, Conference Abstract: Computational and systems neuroscience*, doi: 10.3389/conf.neuro.06.2009.03.069

Bernacchia A, Naveau P (2007) Detecting anomalous spatial patterns with the cumulant function. *Geophysical Research Abstracts*, 9:06806

Bernacchia A, Amit DJ (2005) Network model for learning and memory of highly correlated morphed faces. *Rev Neurosci*, 16 Suppl 1:S9-S10

Bernacchia A, Yakovlev V, Orlov T, Hochstein S, Amit DJ (2003) Behavioral analysis of multiple memory tasks in monkeys. *Neural Plast*, 10:185

Yakovlev V, Hochstein S, Orlov T, Zohary E, **Bernacchia A**, Amit DJ (2003) Multi-item working memory in macaque monkeys. *Perception*, 32:93

PUBLICATIONS

Bernacchia A, Seo H, Lee D, Wang XJ (2011) A reservoir of time constants for memory traces in cortical neurons. *Nature Neuroscience*, 14:366-372.

Bernacchia A, Pigolotti S (2011) Self-consistent method for density estimation. *Journal of the Royal Statistical Society B: Methods*, 73:407-422.

Bernacchia A, Wang XJ (2011) Decorrelation by recurrent inhibition in heterogeneous neural circuits. *arXiv:1107.3111*.

Barra A, **Bernacchia A**, Contucci P, Santucci E (2011) On the equivalence of Hopfield Networks and Restricted Boltzmann Machines. *arXiv:1105.2790*.

Bernacchia A, Naveau P, Vrac M, Yiou P (2008) Detecting spatial patterns with the cumulant function. Part II: Application to El Nino. *Nonlinear Processes in Geophysics*, 15:169-177.

Bernacchia A, Naveau P (2008) Detecting spatial patterns with the cumulant function. Part I: The theory. *Nonlinear Processes in Geophysics*, 15:159-167.

Bernacchia A, Amit DJ (2007) Impact of spatiotemporally correlated images on the structure of memory. *Proc. Natl. Acad. Sci. USA*, 104: 3544-3549.

Yakovlev V, **Bernacchia A**, Orlov T, Hochstein S, Amit DJ (2005) Multi-item working memory - a behavioral study. *Cerebral Cortex* 15: 602-61 5.

Amit DJ, **Bernacchia A**, Yakovlev V (2003) Multiple-object working memory - A model for behavioral performance. *Cerebral Cortex* 13: 435-443.

REFERENCES

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Research Plan

The goal of my research is to uncover the neural circuit mechanisms of cognitive functions. What is the structure of neural circuits necessary to perform cognitive functions? How does this structure self-organize in the brain? To answer these questions, I study the dynamics of neural activity in subjects engaged in cognitive tasks. The electrical activity of neurons shows a complex dynamics encompassing a wide range of timescales, and the details of this dynamics tell us invaluable information about the underlying neural circuitry. However, neural activity is noisy and interpreting the neurobiological observations requires state of the art statistical and modeling techniques. Over the next years, it will be essential to develop new mathematical descriptions to make precise hypotheses and predictive models of neural computation.

My academic background and research experience put me into an excellent position to pioneer and contribute to this research. During my academic career, I have developed, analyzed and simulated computational models of neural circuits, and collaborated with experimental laboratories in testing those models. I have designed novel methods for the statistical analysis of complex data, and I have unraveled key mechanisms controlling the dynamics of neural circuits. I received my Ph.D. at La Sapienza University of Rome, training in Theoretical Physics and Computational Neuroscience under the supervision of Daniel Amit, and collaborating with neurobiologists Volodya Yakovlev and Shaul Hochstein at the Hebrew University of Jerusalem. Following my doctorate, I broadened significantly my skills in statistics by participating in a two-year project focused on the methods for analyzing large datasets, in collaboration with Philippe Naveau at the CNRS of Saclay, France. Currently, I am a postdoctoral fellow at Yale University, working with neurobiologists Xiao-Jing Wang and Daeyeol Lee. The interdisciplinary environment at the Yale Medical School has greatly increased my knowledge in Biology and improved my communication skills.

In the following sections I briefly outline three lines of research that I intend to pursue as an independent investigator.

1) Neural computation on multiple timescales.

The information about multiple events, such as stimuli, actions and their outcomes, has to be integrated in order to form a decision. Depending on the task, this information is integrated for short or long timescales: If the environment offers stable and reliable contingencies, information should be accumulated for long time before making a decision; Conversely, if the environment undergoes quick changes, decisions should be taken on the basis of the recent evidence (Behrens et al 2007). The behavior observed in mental and neurodegenerative diseases is often characterized by inadequate decision-making (Gleichgerricht et al 2010): the inability to follow long timescales may lead to impulsive behavior (e.g. in ADHD and bipolar disorder), while the inability to rely on short timescales, when appropriate, may result in perseverant behavior (e.g. in frontotemporal dementia).

A few studies have estimated those timescales by examining the performance of primates in decision-making tasks (Lau & Glimcher 2005, Corrado et al 2005, Kennerley et al 2006). Neurophysiological studies have shown that neural activity responds to actions and rewards, but no attempt was made to determine the timescales of neural responses (Barracough et al 2004, Samejima et al 2005, Seo & Lee 2007, Histed et al 2009, Bromberg-Martin 2010). My recent work has introduced a new model of neural responses that has allowed measuring the timescales of temporal integration in single neurons (Bernacchia, Seo, Lee & Wang 2011). This study has shown that different neurons of the primate cortex integrate rewards on very different timescales, and that those timescales are related

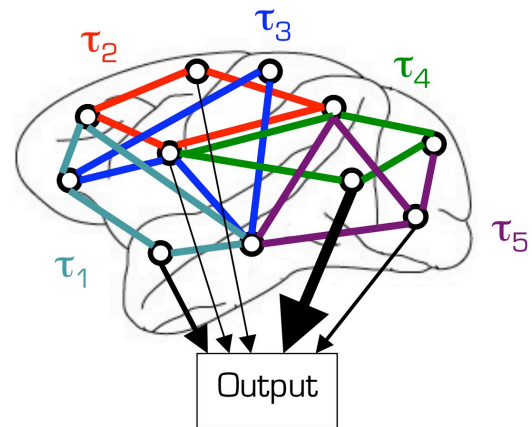


Figure 1: A schematic picture of the working hypothesis of research project (1). The primate cortex includes different neural circuits (five in the picture, in different colors), each characterized by a different integration timescale τ . The output module, responsible for the animal's behavior, selects the appropriate timescale for a given task by modifying the output synaptic weights (black arrows).

to primate behavior.

These findings raise the possibility that a collection of timescales is available across cortical neurons, and a suitable output module may flexibly select the correct timescale for a given task (see Fig.1). This research project will investigate the following questions: do those timescales belong to a permanent collection to be exploited at the present convenience, or does the distribution of timescales depend on the task demands? Which are the neural mechanisms underlying those timescales and their selection for behavior? The first question will be addressed by data analysis, in collaboration with the neurobiologists Daeyeol Lee at Yale University and Kenji Doya at the Okinawa Institute of Science and Technology, Japan. I will determine which are the distributions of timescales in the cortex and basal ganglia during decision-making tasks, and how they change as a consequence of learning. Theoretical analysis and computer simulations of neural circuits will address the second question. I will study a spiking network model of the cortex and the basal ganglia, with a focus on the effect of reward on dopamine and cortico-striatal synaptic plasticity. I expect dopamine-dependent synaptic plasticity to implement the timescale selection in the output module (see Fig.1). While a specific plasticity model may fail to reproduce the expected outcome, different competing models are currently available and this theoretical work will help solving the controversy of which synaptic mechanism is useful for behavior. The ultimate goal of the project is to establish how the brain computes and makes decisions on multiple timescales.

2) Complex dynamics in neural circuits.

The second research project will investigate temporal integration properties of neural circuits characterized by different architectures. The brain is a complex and non-linear system characterized by different dynamical phases; Although the neural dynamics has been successfully described in terms of “relaxation” to a stable state in some studies (Bernacchia, Seo, Lee & Wang 2011), other tasks may require the existence of multiple stable states. For example, the quick and persistent response of neurons to stimuli in working memory tasks seems to be inconsistent with a single stable state (Fuster & Jervey 1981, Funahashi et al 1989, Romo et al 1999). This type of dynamics has been modeled by “attractor” neural networks, where the neural response corresponds to a jump from a given stable state (attractor) to another one, representing the stored memory (my own work on the topic includes Bernacchia & Amit 2007, Amit, Bernacchia & Yakovlev 2003, Yakovlev, Bernacchia, Orlov, Hochstein & Amit 2005). However, those “attractor” models are insufficient to describe neural dynamics, as recent neurophysiological studies suggest that only a few neurons show persistent activity, while others show complex trajectories (Rainer & Miller 2002, Brody et al 2003, Shafi et al 2007, Sigala et al 2008, Machens et al 2010).

Therefore, neither the “relaxation” nor the “attractor” model fully account for the observed data in different tasks. This is not surprising, since the former is characterized by random connections between neurons (see Fig.2a and Sompolinsky et al 1988, Buonomano & Maass 2009), and the latter is characterized by symmetric connections (see Fig.2b and Hopfield 1982), while it is well known that the topology of the cortex is neither completely random nor precisely symmetric (Song et al 2005, Perin et al 2011). Which types of connectivity structures account for the complex trajectories of neural activity observed in neurophysiological data? This project will address this question by theoretical analysis and computer simulations of different neural circuit architectures, with the goal of reproducing the observed neural dynamics. The theory of random matrices and the theory of disordered systems will be applied on this purpose (my own work on the topic includes Bernacchia 2011, Barra, Bernacchia, Contucci, Santucci 2011).

For example, a novel type of architecture is based on the assumption that connections between

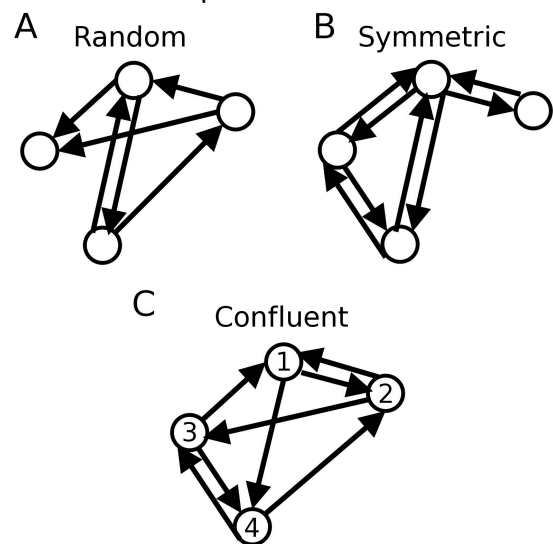


Figure 2: Three examples of connectivity structures investigated in research project (2). A: Random connectivity. Neural activity relaxes to a unique stable state. B: Symmetric connectivity. Neural dynamics admits multiple stable states. C: The connectivity is neither completely random nor precisely symmetric. Projections from a neuron to a pair of other neurons successively merge into a fourth neuron (e.g. projections from neuron 4 spread into neurons 2 and 3 and then merges into neuron 1).

neurons are confluent. In Fig.2c, neuron 4 projects to neuron 2 and 3, whose projections then merge into neuron 1. Since the input neuron (4) may be different from the output neuron (1), this type of architecture includes symmetric connections but also asymmetric ones, and promotes clusters of neuronal assemblies. A preliminary account of experimental data following this architecture has been presented in (Bernacchia, Seo, Lee & Wang 2011). While a specific neural circuit architecture may fail to reproduce those dynamics, different competing structures are currently available and this theoretical work will help solving the controversy of which structure is responsible for the observed dynamics of neuronal assemblies. The ultimate goal of the project is to establish the principles governing the interactions in neural circuits.

3) Evaluating dynamic firing rates.

The third research project will focus on the design of novel statistical techniques for multivariate analysis and density estimation. The main theme of my research is that the dynamics of neural activity is an essential feature of neural processing. This dynamics is often described in terms of firing rates, obtained by counting the number of action potentials in a sequence of time intervals (bars in Fig.3a). In order to distinguish fine temporal changes in activity and obtaining a better temporal resolution, the activity is modeled by a continuous function, given by the probability of an action potential being emitted at each instant of time (line in Fig.3a). In absence of a principled model, the estimation of this probability is a hard problem, since it requires a regularization procedure such as the adjustment of the bin size, bandwidth or cutoff frequency.

In my recent work, I developed a self-consistent procedure to estimate a density distribution from data points, which does not require any adjustment of parameters (Bernacchia & Pigolotti 2011). The method determines the optimal estimate of the density from a series of iterative estimates, where the final and unique outcome is obtained analytically, therefore without implementing any iteration (an example is shown in Fig.3b). The method allows fast and reliable density estimation with unprecedented accuracy, and represents a novel approach to various problems in statistical inference. The research project will focus on two separate aims, one in data analysis and one in mathematical statistics. First, I will apply the self-consistent method to the estimation of dynamic firing rates in neuronal data. Once accurate estimates of the firing rates will be achieved, the relation of this dynamics with stimuli and behavior will be assessed with higher sensitivity and statistical power than ever before. For example, one application could be the characterization of the linear response of neurons to sensory stimuli. This goal will be accomplished in collaboration of different neurophysiological laboratories providing with the neural data.

In recent years, the development of different technologies allowed measuring the simultaneous activity of multiple neurons (e.g. multi-electrode arrays, two-photon microscopy). In my previous work, I have explored multivariate optimization in high-dimensional datasets (Bernacchia & Naveau 2008, Bernacchia et al 2008). Therefore, the second aim of the research project is to generalize the self-consistent method to multivariate data, in order to fit the simultaneous dynamics of the activity of multiple neurons. This goal will be accomplished by generalizing the mathematical techniques used in the derivation of the self-consistent estimate, from a scalar to a vector space. Several benchmark multivariate datasets will be considered for testing the effectiveness of the new approach. While the method may not work for all kinds of probability distributions, the project will help determining the correct hypothesis under which different methods should be applied. The ultimate goal of the project is to provide an automatic and universal tool for assessing dynamic firing rates in neural data.

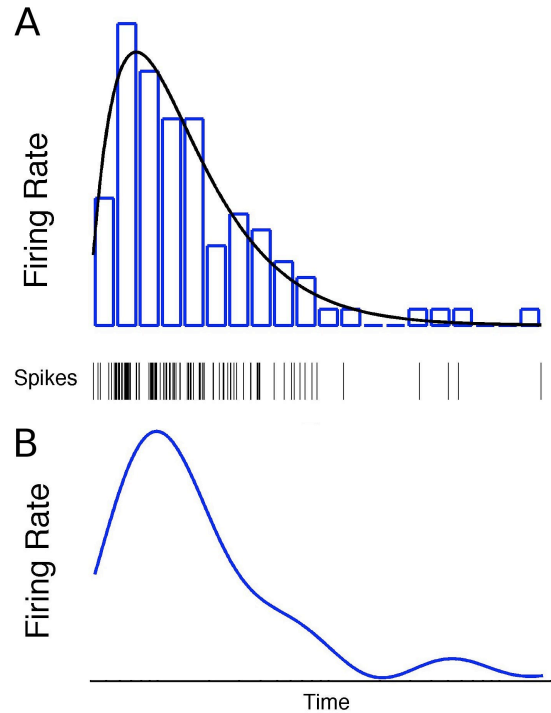


Figure 3: Firing rate estimates from a sequence of action potentials. A: Bars – action potential counts in separate bins. Line – continuous probability of spike emission. Spikes: action potentials. B: Self-consistent estimate of the firing rate obtained from the same sequence of action potentials.

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Teaching Statement

I have thoroughly enjoyed my teaching experiences and I regard teaching as a one of the most appealing aspects of an academic career. Over time, I have gained a range of experience both as a course instructor and as advisor of student internships, research projects, and honor theses. During my doctoral studies I worked as a teaching assistant of three undergraduate courses at La Sapienza Università in Rome. These included the following topics: “Physics - mechanics, thermodynamics and electromagnetism”, “Computational physics - numerical simulations” and “Neural networks – modeling brain function”. During my postdoctoral appointment I continued my efforts by teaching two short courses on advanced topics in graduate school: “Methods for the statistical analysis of multivariate data” and “Statistical theory of extreme values”.

I also had the opportunity of tutoring several undergraduate students during their internship in the computational laboratory at Yale University. Some of these projects resulted in honor theses and conference presentations. I have also helped in supervising two graduate students during their doctoral studies, one student in applied mathematics and one in the interdisciplinary neuroscience program. Yale University has several interdisciplinary programs for graduate students, and I participated in the neuroscience program by organizing a few seminar series. The students enrolled in this program regularly visit me to obtain advice on the advancement of their career and research. Those experiences at Yale University have greatly improved my interpersonal communication skills.

In my lectures, I have constantly encouraged students to critically evaluate and discuss scientific research, maintaining an open-minded approach and thinking about alternatives. For example, an important topic that is often overlooked in teaching at the academic level is the progress of disputes between competing scientific theories. The discussion is a fundamental part, since it stimulates the participation of students and, most importantly, it reveals how science makes progress. I have also spent much effort in assessing the work of students. During my Ph.D., I started helping senior lecturers in evaluating written and oral exams, and soon I was assigned the responsibility to determine the final assessment of part of the undergraduate students attending the courses. Beyond the final assessment, I made the highest effort in evaluating the individual learning progress by stimulating the participation of students in class (e.g., discussing how scientific findings relate to their lives, directed writing assignments).

Since the early stages of my career I understood that the challenge for interdisciplinary education is hard but feasible. During my Ph.D., I was told that I could not teach Physics to undergraduate students because, even if I graduated in Physics, the topic of my Ph.D. program was Neurobiology. After some altercation I was able to overcome the dispute and I could assist in teaching the Physics class. This is just a simple example suggesting that academic communities are ready to integrate different disciplines albeit with some struggle. In each one of my appointments I have been actively working on bringing together different types of expertise, especially between theorists (physicists and mathematicians) and experimentalists (biologists), and this is exemplified by my continuous collaboration with experimental laboratories (four

collaborations to date). This is crucial for the progress of biological sciences. For example, recently I received an email from a student who is hesitant on whether pursuing a Ph.D. in experimental or computational neurobiology. The solution to this problem is bringing people working in the two areas as close as possible.

Based on my experience and interest I can teach a variety of courses at the undergraduate and graduate level. I would welcome the opportunity to teach courses that emphasize ties between different disciplines and methodologies. Given my interest in understanding emergent properties of complex system, in particular of brain function, I would be particularly effective in teaching Computational Neuroscience and Computational Biology. However, I am also well prepared to teach courses in Physics (mechanics, thermodynamics, statistical mechanics), Statistics (regression analysis, multivariate analysis, statistical inference) and Applied Mathematics (theory of dynamical systems, theory of stochastic processes, mathematical optimization).

In any type of class, I am enthusiastic about encouraging students to take an approach that is simultaneously critical and open-minded. Mentoring students, helping focus and direct their individual interests in computational biology, and helping them to build skills that will serve their development in research or other pursuits has been among my most rewarding experiences in academics. In addition to my eagerness to teach undergraduates, I look forward to the opportunity to mentor young scientists working with me as graduate students and postdocs. I would like to continue and expand a way of teaching and research supervision that focuses on getting students interested and actively involved in learning in depth and breadth about scientific topics and in conducting high-quality research.