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Dear committee members

Please accept this application for an assistant professor position in biocomplexity.

I am a neuroscientist, combining computational modeling and electrophysiology to understand how neuronal networks generate rhythmic activities. My doctoral work, with Dr. L.E. Moore, focused on how spinal circuits of the Xenopus tadpole generate swimming activity. I am now finishing my post-doc, working with Drs. Michael O'Donovan and John Rinzel on the generation of spontaneous episodic activity in the developing spinal cord.

Best Regards,

Joël Tabak

Research Interests

Summary
A key problem in neuroscience is to understand the cellular basis of behavior. This is a fascinating problem, because a given activity pattern can be produced through interactions between different levels of complexity. Vertebrate neural networks have very diverse architectures, are composed of many thousands of neurons of many different types connected through various classes of synapses, and the properties of each neuronal type can be tremendously complex. In addition, the neurons and their connections are plastic. Despite this complexity, can we uncover principles governing the way networks generate activity?

I am addressing this problem by studying the spinal networks that generate rhythmic, locomotor-like activity (Central Pattern Generators or CPGs). Rhythmic motor behaviors have long been recognized as model systems for addressing questions of network function because of their unique experimental advantages. These include: a well characterized cyclical output; the ability to produce the output when maintained *in vitro*; known anatomical locations of the networks; and the ability to study these networks during development, as they become more complex and acquire their mature characteristics.

Even the relatively simple networks of the spinal cord involve a variety of nonlinear biophysical processes. To understand how these processes cooperate to generate rhythmic activity, computational modeling is an essential tool. However, it is important that the computational models be related to experimental data. During my postdoc, I have been combining these approaches to analyze the spontaneous rhythmic output of the developing spinal cord of the mouse and the chick embryo. I now plan to extend this work to address fundamental questions about the mechanisms of locomotor-like activity in the spinal cord. Specifically, I want to build on the results of my post-doctoral work concerned with the mechanisms of spontaneous episodic activity to ask the following major questions:

1) How does the mature vertebrate spinal CPG generate rhythmic locomotor activity? Is the mechanism for rhythm generation based on purely excitatory networks, as in the immature circuits, or do inhibitory connections play a role in rhythm generation? This is an important question because most networks of the mammalian central nervous system exhibit spontaneous episodic activity early in development, due to the same general mechanism. Episodic activity stops and the networks acquire their mature characteristics after inhibitory connexions have developed. Does inhibition fundamentally alter network mechanisms, or does it simply set the excitability level and coordinate distinct excitatory subnetworks whose outputs are still governed by the same general principles observed in immature networks?

2) How does the spontaneous activity occurring during development influence the formation of the circuits that will ultimately generate locomotor activity in the adult? This question naturally arises from the previous one, because the development of inhibition and other developmental changes that contribute to network maturation are thought to be activity-dependent.

Mechanisms of rhythm generation in locomotor CPGs
Studies of vertebrate CPGs have been very much influenced by work in invertebrate CPGs that concluded that complex oscillatory circuits are made of elementary building blocks: individual synapses and voltage-gated currents that together produce a rhythmic activity. Often this involves pacemaker currents or networks using inhibitory connections. However, vertebrate networks are

large scale. The application of concepts from invertebrate CPGs to vertebrate CPGs has not been very successful so far. We still do not know the mechanism(s) responsible for the generation of rhythmic alternating activity in the vertebrate spinal cord. In particular, despite numerous experiments with various preparations, the role of inhibitory connections in rhythm generation is not well understood.

I first plan to investigate the hypothesis, derived from my post-doctoral work, that rhythmic activity is produced by excitatory subnetworks within the spinal cord, that employ the same kind of mechanism as has been proposed to underlie the spontaneous activity characteristic of the developing spinal cord. According to this idea, the function of inhibition would be to coordinate the activity of these subnetworks and set their excitability levels. Consistent with these ideas, disinhibiting the spinal circuits in the neonatal mouse spinal cord leads to an episodic bursting activity with characteristics of the embryonic episodic activity. These preliminary data show that the immature mechanism can be unmasked in a more mature circuit and emphasizes a continuity between immature and mature networks.

How do we distinguish a mechanism based on purely excitatory network from a mechanism where reciprocal inhibition is essential for rhythm generation? One reason it has been so difficult to test hypotheses and models concerning the functioning of CPGs is that experimental interventions (surgical ablations, pharmacological blockade) designed to investigate some components of the CPG may profoundly change the network, qualitatively affecting the mechanism that one attempts to study.

An alternative strategy is to use small perturbations which do not alter the primary mode of network operation, but which nevertheless can provide important information about how the network operates. One experimental way to accomplish this is to partially, rather than totally, block synaptic currents or synaptic function, thereby minimizing the disturbance of network function. Can such small interventions in network operation provide useful information? Perhaps surprisingly, the answer is yes. During my postdoctoral work, I used this approach to distinguish between synaptic and cellular depression mechanisms for the termination of spontaneous episodes of activity (Tabak et al. 2000).

I now intend to apply this strategy to establish if synaptic inhibition is involved in rhythmogenesis in the mammalian spinal cord. To do so, I will design model networks with similar architecture, including reciprocal inhibition, but differing in the way they generate rhythmic activity. Partial block of certain cellular or synaptic parameters may induce different changes on the characteristics of the activity such as the oscillation frequency. Once these critical parameters (the ones that lead to opposite changes in the different networks) are identified, I will conduct experiments on the neonatal mouse spinal cord where the physiological correlate of the critical model parameters are experimentally altered (partial block, partial lesion), to select the right model. This will allow me to validate specific sets of hypotheses about rhythm generation before developing more detailed model of the spinal CPGs.

Activity-dependent development of locomotor CPGs

A universal feature of neural networks is their plasticity. Network activity alters network properties through various mechanisms, including Hebbian learning and homeostatic plasticity. These network alterations in turn change network activity. A complete understanding of spinal motor network function must include an analysis of how network activity feeds back to regulate and stabilize the very networks responsible for the activity. This fundamental and reciprocal interdependence of network architecture and network activity is one that is rarely addressed in studies of mammalian CPGs. Developing systems such as the embryonic spinal cord are

spontaneously active over a period of a few days during which the spinal networks mature into circuits that can generate locomotor rhythms. Thus they provide a unique opportunity to understand how activity regulates/transforms itself through network alterations.

There is evidence that spontaneous episodic activity drives some aspects of network maturation. During a spontaneous episode, many neurons are activated together and the level of correlation between the activity of neurons may determine how the synapses between these neurons will be strengthened or depressed. There is also evidence that calcium entry in neuronal cells during activity can modify neuronal properties. Are these modifications in synaptic and cellular properties important features of network maturation? How do they shape the network and its activity?

In order to explore the impact of these activity-dependent transformations of the spinal circuitry, I will use a population model network that generates spontaneous episodes of activity and introduce some activity-dependent rules such as spike timing dependent synaptic plasticity. My collaborators (B Vladimirski and J Rinzel) and I have already developed a population network that generates episodic activity through the same mechanism as in the mean field model we have used previously. I will add long term synaptic plasticity to this model, which is expected to lead to strengthening of some synapses and weakening of other synapses. One crucial question that I plan to investigate is whether or not such alterations in the strength of neural connections will result in the differentiation and formation of subnetworks. Such subnetworks, in different parts of the spinal cord (rostral/caudal; left/right), might retain their capacity for rhythmicity and become coordinated by synaptic inhibition. If the modeling suggests this as a plausible outcome of adding plasticity to our current models, then it should be possible to identify ways of compromising these developmental transformations experimentally.

An attractive preparation to carry this type of experiment is the organotypic culture of the whole spinal cord. Such a preparation was developed in the Laboratoire de Neurobiologie des Réseaux, Université de Bordeaux 1. In this developing spinal cord culture, spontaneous activity evolves similarly to the activity in intact mouse spinal cord. This culture preparation, which can be grown on microelectrode arrays, will allow me to record and perturb the activity continuously during the period over which the network switches from generating spontaneous activity to being able of generating locomotor rhythm. This will allow me to validate the results obtained from the modeling studies. I have no direct experience with organotypic culture, but I will first collaborate with researchers from the Laboratoire de Neurobiologie des Réseaux and later develop this preparation in my laboratory. Two researchers from this laboratory (B Yvert and P Branchereau) and myself have been awarded a three-year grant to start addressing these questions (Action Concertée Incitative Neurosciences Intégratives et Computationnelles, 2003).

Previous Research Experience

Doctoral Research: Study of a simple rhythm generating circuit

The *Xenopus* embryo (a tadpole) swims by rhythmically moving its tail left and right. This rhythmic, alternating activity of left and right muscles is generated by networks in the spinal cord called central pattern generators (CPGs). One important feature of spinal CPGs is the reciprocal inhibition between the left and right parts of the circuit. This reciprocal inhibition is responsible for the alternation between the two sides. In addition to coordinating the left and right sides, it has been proposed that reciprocal inhibition is essential in the generation of the oscillating activity

itself. Using a realistic model of a spinal segmental CPG, I showed that adding a non-linearity to the excitatory synapses (the NMDA channel voltage-dependency) could allow each side of the network to become capable of generating rhythmic activity. Therefore, reciprocal inhibition may not be necessary for rhythm generation in this circuit. The possible role of inhibition in the genesis of oscillatory activity in vertebrate CPGs is still an open question.

Postdoctoral Research: Spontaneous episodic activity in the developing spinal cord

Early in development, neural networks are purely excitatory because the chloride-mediated transmission which underlies synaptic inhibition in more mature circuits has excitatory effects. This greatly simplifies the analysis of network operation. Due to the predominance of excitation, developing networks thus generate spontaneous activity. This activity is episodic. In the embryonic chick spinal cord, episodes of activity can last one minute and are separated by silent intervals lasting up to about 15 minutes, an unusually slow time scale. During an episode, the activity is oscillatory, with a period of about 1 second. In the absence of synaptic inhibition, what mechanisms generate these multiple time scale rhythms?

To understand these mechanisms, I have used a conceptual model based on a purely excitatory network with activity-dependent mechanisms that depress network excitability. The model only takes into account the averaged (over time and over the neuronal population) activity in the network. This “mean field” approach has allowed a qualitative understanding of the dynamical features of the spontaneous episodic activity. The episodes are terminated by a slow activity-dependent depression of network excitability. When the network has recovered from this depression, a new episode can occur. Similarly, a faster depression can explain the fast rhythm observed during the episodes. This model leads to several predictions.

One prediction is the existence of a statistical relationship between episode duration and interepisode interval. I showed using long recordings of spontaneous activity that there is a correlation between burst duration and preceding (but not following) interburst interval. This implies that the system is “reset” after an episode, that is, episodes always terminate at a fixed level of depression. Episode termination is thus a deterministic event, while episode onset is stochastic. A similar mechanism for the regulation of episodic activity has been proposed for other developing/excitatory systems (retina, cortex, hippocampus) and indeed a similar correlation between episode duration and interepisode interval has been found in these systems. Thus, despite greatly differing architectures, all these developing networks share a common mechanism for generating episodic activity.

The model also explained a surprising result. When glutamatergic connections are blocked, activity stops for a while but then reoccurs as regularly as in control conditions. The model based on activity-dependent *synaptic* depression reproduces this result when a parameter describing the average connectivity is decreased. After the connectivity is decreased, the network model cannot sustain activity anymore. In the absence of activity, synaptic efficacy in the network recovers from depression as in control conditions (before the connectivity decrease), but because activity does not start, synaptic efficacy can continue to increase to levels higher than in control. When the level of synaptic efficacy is such that it compensates the decreased connectivity, the activity reoccurs. This predicts that after experimental glutamatergic blockade the unblocked synaptic pathways should operate at a higher level of efficacy, which I verified experimentally. Thus, the very mechanisms that regulates episodic activity (synaptic depression) provides an intrinsic robustness to the activity. This is important since activity is thought to play a role in circuit maturation. Finally, a model for which the depression of network excitability is cellular, instead of synaptic, does not predict this behavior. Therefore, this experiment allowed us to distinguish between synaptic and cellular mechanisms of activity-dependent depression.

Teaching Interests

I am highly interested in teaching a neuroscience course for students majoring in physics, maths or computer science. This course can introduce students to neurophysiology, from cellular phenomenons (electrical properties of neurons, action potential generation, synaptic transmission, plasticity) to systems behavior. The systems reviewed will be well defined circuits with well defined output, such as locomotor circuits or the integrator circuit of the oculomotor system. They will serve to illustrate ideas about how cellular and network properties interact in the process of creating the system's activity. In the course, various techniques will be introduced (electrophysiological recordings, calcium imaging) but the emphasis will be on using modeling approaches as essential tools to understanding of these systems.

Therefore a large amount of time will be devoted to running model simulations (using software such as NEURON and XPPAUT). Numerical "experiments", where parameters can be varied freely will allow students to develop intuition and identify the key parameters and mechanisms. Then, methods of analysis for nonlinear systems will be introduced (phase plane analysis). Finally, model outputs will be compared to real data to show the models' limitations. If possible, simple experiments will be conducted by the students, to develop a workflow between modeling and experimentation.

My teaching experience includes lectures on the Hodgkin-Huxley model of action potential generation and on the vestibular system, for the neuroscience graduate program at the University of Maryland (program director: Avis Cohen).