Présentation détaillée du projet pour l'AAP « Neurosciences, neurologie et psychiatrie » 2006

Acronyme du projet : **HR-Cortex**

1 – Objectifs et contexte : *(2 pages maximum en Arial 11, simple interligne)*

On situera le projet dans le contexte international en y précisant les objectifs et les enjeux.

Ce texte sera rédigé en anglais.

2 – Description du projet et résultats attendus *: (8 pages maximum en Arial 11, simple interligne)*

On décrira le déroulement prévisionnel et les diverses phases intermédiaires ainsi que les méthodologies employées. L'originalité et le caractère ambitieux du projet devront être explicités. L'interdisciplinarité et l'ouverture à diverses collaborations seront à justifier en accord avec l'orientation du projet. Le rôle des équipes dans les différentes phases du projet devra être précisé et la valeur ajoutée des collaborations entre les différentes équipes sera argumentée. Les moyens demandés devront être en accord avec les objectifs scientifiques du projet.

Ce texte sera rédigé en anglais.

1 - Background and Objectives

This proposal will focus on two different aspects of the electrophysiology of cortical neurons: first, the study of high-conductance states, similar to those found in vivo, and second, the measurement of conductances in various situations in vivo. The latter is of considerable interest for studying the mechanisms underlying the response selectivity of neurons in primary sensory cortices.

1.1 High-conductance states

Neurons are subject to many different sources of noise(*1*), which in combination with their excitability may significantly alter their integrative properties (reviewed in Destexhe et al, 2003(*2*)). Of these different sources of noise, synaptic noise is undoubtedly the most prominent one in activated states. In the cortex, synaptic noise originates from the seemingly random and sustained firing of individual cortical neurons (5 to 40~Hz in awake animals) (reviewed in Steriade, 2001(*3*)), combined with their remarkably dense connectivity (tens of thousand synaptic inputs per neuron; reviewed in Braitenberg & Shutz, 1998(*4*)). This intense synaptic activity sets the cellular membrane into a high-conductance state, in which the input resistance is reduced by 3 to 5 times compared to quiescent states(*5*).

A method for studying high-conductance states is through re-creating those states artificially by injecting conductances in vitro. This is possible through the dynamic-clamp technique, which was introduced a decade ago(*6, 7*) and is equivalent to adding a "virtual" conductance in the membrane of a real neuron by injecting a current into the membrane which depends on the actual membrane potential. Implementing this paradigm in cortical slices(*8-12*) yields a state of stochastic activity similar to that observed in vivo, with a depolarized and fluctuating membrane potential, irregular firing, and a markedly reduced input resistance.

However, the dynamic-clamp technique suffers from one main limitation, namely that the recording electrode is also used to inject current. The limitation arises from the fact that the electrode introduces a bias in the measurement(*13*). Single-electrode voltage-clamp measurements in vivo also suffer from the same limitation. A common way to circumvent this electrode bias is to use compensation of resistance and capacitance on the amplifier, but these compensations are incomplete and subjective. Another way is to use two electrodes, one to record and another one to inject current. Currently, this technique is mostly used in invertebrate ganglia and is not realizable in the neocortex in vivo.

In the present proposal, we plan to investigate a method to circumvent these difficulties and perform high-resolution current-clamp, dynamic-clamp and voltage-clamp recordings using single electrodes. Moreover, we will also propose methods to directly extract information about network activity from the fluctuations of conductances, for which no method is presently available.

1.2 – Conductance measurements

Measuring conductances in central neurons in vivo is essential to understand the response selectivity of those neurons. Response selectivity can arise from particular timings of excitation and inhibition(*14-17*), which can be amplified by intrinsic conductances(*16*). Conductance measurements can be realized by reconstructing current-voltage relations from V_m activity(*14, 18*) or by using the statistics of the V_m fluctuations(*19*). These methods suffer from one severe limitation, namely that it is necessary to accumulate statistics over many trials and different levels of polarization, which necessarily mean that information about the variability unlocked to the stimulus is lost. A possibility is to use single-electrode voltage-clamp measurements via patch electrodes(*14*), but this technique is difficult to implement in vivo, and it is not possible to extract excitatory and inhibitory conductances from a single-trial measurement (since at least two clamps must be performed). Moreover, most of in vivo recordings are made using sharp electrodes, which introduce considerable bias (see above), and make the reliability of voltage-clamp uncertain which requires to use discontinuous

methods(*20*) which are necessarily at low temporal resolution (2-3 KHz). In the present proposal, we address those limitations and propose several methods to reliably record conductances in vivo.

1.3 – Objectives of the proposal

This proposal will combine different expertises, such as mathematics, computer science, computational neuroscience and electrophysiology (in vitro and in vivo), to yield accurate and reliable methods to properly characterize high-conductance states in neurons. We plan to address several of the caveats of present recording techniques, namely (1) the impossibility to perform reliable high-resolution dynamic-clamp with sharp electrodes, which is the intracellular technique mostly used in vivo; (2) the unreliability and low time resolution of single-electrode voltage-clamp recordings in vivo; (3) the impossibility of extracting single-trial conductances from V_m activity in vivo. We propose to address these caveats with the following goals:

(1) Obtain high-resolution recordings applicable to any type of electrode (sharp and patch), any type of protocol (current-clamp, voltage-clamp, dynamic-clamp) and different preparations (in vivo, in vitro, dendritic patch recordings).

(2) Obtain methods to reliably extract single-trial conductances from V_m activity, as well as to "probe" the intrinsic conductances in cortical neurons. These methods will be applied to intracellular recordings during visual responses in cat V1 in vivo.

(3) Obtain methods to extract correlations from V_m activity and apply these methods to intracellular recordings in vivo to measure changes in correlation in afferent activity.

(4) Obtain methods to estimate spike-triggered averages from V_m activity and obtain estimates of the optimal patterns of conductances that trigger spikes in vivo. These results will be integrated into computational models to test mechanisms for selectivity.

In all of these methods, we take advantage of the *real-time feedback* between a computer and the recorded neuron. This real-time feedback will be used to (a) design a new type of recording paradigm, which we call *Active Electrode Compensation* (AEC), and which consists in a real-time computer-controlled compensation of the electrode artefacts and bias which currently limit recording precision; (b) to use the AEC method to improve current-clamp, voltage-clamp and dynamic-clamp recordings of cortical neurons; (c) use this method as an essential tool to design methods for estimating conductances and statistical characteristics of network activity from intracellular recordings.

Thus, we expect this project to provide three main contributions: (1) It will provide technical advances in the precision and resolution of several currently-used recording techniques, such as dynamic-clamp and voltage-clamp, which are currently limited. We aim at obtaining high-resolution (>= 20 KHz) reliable measurement or conductance injection. This advance should be of benefit for in vivo and in vitro electrophysiologists. (2) It will enable us to perform high-resolution conductance measurements in high-conductance states in vivo and in vitro and better understand this type of network activity. (3) It will enable us to better understand the spike selectivity of cortical neurons, by directly measuring single-trial conductances underlying visual responses, as well as the conductance time courses linked to the genesis of spikes. Those measurements will be directly integrated into computational models. The mechanisms of spike selectivity in cortical neurons is still a subject of intense debate, and we expect to provide here crucial measurements, which we hope will help us better understand input selectivity in visual cortex.

2 - Project Description

2.1 - Active Electrode Compensation (AEC)

2.1.1 – Principle

The principle of the AEC method is to increase the resolution of intracellular recordings by performing a computer-controlled active compensation for electrode transients. Because these transients are one of the main limiting factor for the accuracy of recording techniques, and in particular for dynamic-clamp and voltage-clamp, the AEC should have a high impact on these recording techniques, and enabling to perform protocols that would not be possible before.

The essential idea behind the method is to represent the electrode by an arbitrarily complex linear circuit, extract the properties of this circuit for each particular recording, and actively compensate for the effect of the electrode by subtracting the voltage drop through this circuit from the recording. The voltage across the electrode U_e is modelled as the convolution of the injected current I_e and a kernel K_e which characterizes the electrode:

$$U_e(t) = (K_e * I_e)(t) = \int_0^{+\infty} K_e(s) I_e(t-s) ds$$

This formulation encompasses any linear model, e.g. a circuit with several resistances and capacitances. The procedure consists in two passes: 1) measure the electrode kernel K_e using a noisy signal as a probe, 2) inject and record at the same time in continuous mode, with the true recording obtained by subtracting the voltage across the electrode U_e from the raw recording. The compensation involves a digital convolution which is performed in real time by a computer.

The method differs from bridge compensation mainly in the fact that the electrode model is non-parametric, and therefore can faithfully account for non-ideal electrodes. Because bridge compensation cannot fully compensate for electrode transients, it cannot be used for injecting noisy conductances. On the other hand, the discontinuous current clamp (DCC), which is commonly used as an alternative to bridge compensation, is noisy and limited in temporal resolution by the properties of the electrode (in our experiments with sharp electrodes, the maximum sampling rate was 2-3 kHz); it also exhibits artefacts due to the approximations underlying the method (namely, that the time constant of the electrode must be several orders of magnitude smaller than the membrane time constant). Here with AEC, the sampling rate is only limited by the speed of the computer (in our preliminary experiments the rate was 10 kHz) and computer models have shown that recordings are more faithful than with DCC.

2.1.2 – Preliminary Results

Figure 1.A shows an electrode kernel recorded with AEC in a cortical neuron in vitro (sharp electrode), which is close to but not exactly exponential (which corresponds to a simple electrode model with a resistance and a capacitance). Fig. 1.B shows a numerical simulation of an injection of a square wave of conductance with AEC and DCC (blue), compared to the analytical solution (red). Fig. 1.C shows the response of a cortical neuron in vitro to white noise injection, sampled at 10 kHz, with bridge compensation. Without AEC compensation (blue), the fast frequencies of the signal induce dramatic transients due to the electrode artifacts. These transients are so large that it is impossible to distinguish them from real spikes. With AEC compensation (red), most the artifacts are compensated, and one can clearly see 3 spikes in this case. These results clearly show that the AEC works in practice (it was tested so far in more than 15 cells), and is superior to both DCC and bridge compensation. Both numerical simulations and the dynamic-clamp experiments were run using NEURON(*21*). These first results were presented at the SfN Neuroscience conference in Washington (2005)(*22, 23*).

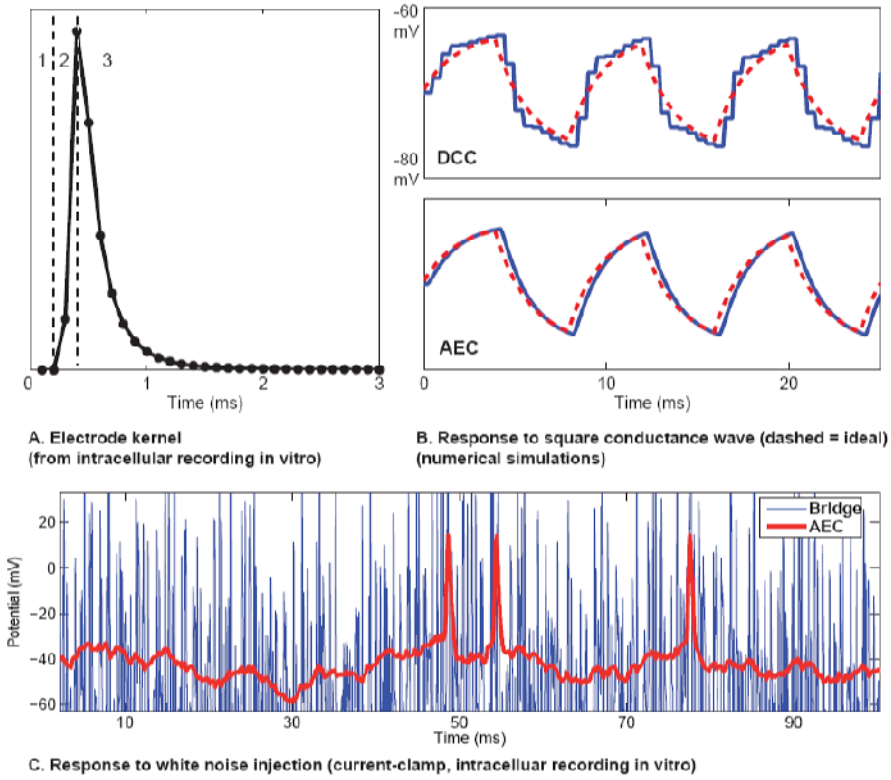

Figure 1 – Active Electrode Compensation

2.1.3 – Project outline

(1) *Theoretical development of the AEC method*. We will develop the AEC method, including designing automatic procedures to estimate the parameters of the compensation, and estimating its robustness to various conditions. We will also develop the voltage-clamp AEC method, which will require modifying the AEC specifically for this case. This part needs expertise in mathematics, computational neuroscience and knowledge of the electrodes and amplifier setups. It will be performed in collaboration between INRIA and UNIC.

(2) *Test of the AEC method using numerical simulations.* We will test the AEC method numerically by designing computational models of the different modes of recordings (current-clamp, DCC, voltage-clamp, DVC, dynamic-clamp). This part will be performed conjointly between INRIA and UNIC.

(3) *Test of the AEC method in current-clamp and dynamic-clamp in vitro.* The AEC will be tested by using several protocols, in both sharp and patch recording conditions, including dendritic patch recordings. We will test injection of white noise, colored noise, and conductance pulses. In situations where the analytic expression of the V_m is know, it will be compared directly to the recordings, using the different techniques (such as DCC, dynamic-clamp). The protocols will be designed by INRIA and realized experimentally and computationally at UNIC.

(4) *Test of the AEC method in voltage-clamp in vitro.* The AEC will be tested in vitro in voltage-clamp mode. We will use both sharp and patch recordings of miniature events or extracellularly elicited PSPs, which will be recorded using classic voltage-clamp methods. The difference with AEC voltage-clamp will be quantified to evaluate the gain of the method in resolution. This part of the project will be performed at UNIC, with help from INRIA.

(5) *Test of the AEC method in voltage-clamp in vivo.* We will test the voltage-clamp methods in intracellular recordings of V1 neurons in vivo. Several methods will be

compared, such as extracting conductances from V-I curves, discontinuous voltage-clamp (DVC) and AEC voltage-clamp. This part will be performed at UNIC with help from INRIA.

2.2 – Extraction of conductances from single trials

2.2.1 – Principle

The principle of this method is to inject white noise into the membrane of the recorded neuron, and from the voltage response to white noise, it is possible to extract conductances with reasonable accuracy. The interest of such a method is considerable, since it could allow, for the first time, to perform extraction of excitatory/inhibitory conductances from single-trials. The impact of such measurement method is potentially important in sensory physiology. It will allow us to study presently unanswered questions, such as the trial-to-trial variability of conductance combinations leading to input selectivity in neurons of visual cortex.

The method is based on an error minimization procedure, in which the INRIA team has a great expertise(*24-28*) (e.g. for functional and diffusion imaging problems, EEG and MEG). The start point is to minimize a prediction error on the membrane potential:

$$E = \int (\tilde{V}(t) - V(t))^2$$

where $\tilde{V}(t)$ is the prediction of the membrane potential given current estimates of the excitatory and inhibitory conductances $g_e(t)$ and $g_i(t)$, and V(t) is the actual recorded membrane potential. However, minimizing this error is an ill-posed problem because there are two unknowns for only one observable quantity. The solution we have designed is to inject a noisy probe signal I(t) into the neuron and add a regularity criterion of the type:

$$E_r = a\int g_e'(t)^2 + b\int g_i'(t)^2$$

This criterion formalizes the intuitive idea that the conductances should vary slowly compared to the probe signal I(t). The AEC method makes it possible to use a very fast probe signal such as white noise.

As far as we know, this is the first method ever developed to estimate synaptic conductances from a single trial.

2.2.2 – Preliminary Results

Figure 2 shows this method in a numerical simulation in which we have simulated an AEC recording with an electrode model and a neuron with noisy synaptic conductances (excitatory and inhibitory). The method can recover single-trial conductance traces with reasonable accuracy, but the AEC is required since white noise must be injected (see Fig. 1C).

2.2.3 – Project outline

(1) *Theoretical development of the white-noise injection (WNI) method.* This part will require to elaborate the fitting methods, as well as to test the method numerically using computational models. It will be performed at INRIA, in collaboration with UNIC.

(2) *Test of the WNI method in vitro using known injected conductances.* We will use the dynamic-clamp to inject known patterns of synaptic conductances in neurons in vitro (using both sharp and patch electrodes). The WNI method will then be applied to these recordings, which will be analyzed solely from the V_m activity. This analysis will be realized in different conditions and parameters to evaluate the reliability and robustness of the method. This part will be realized at UNIC, in collaboration with INRIA.

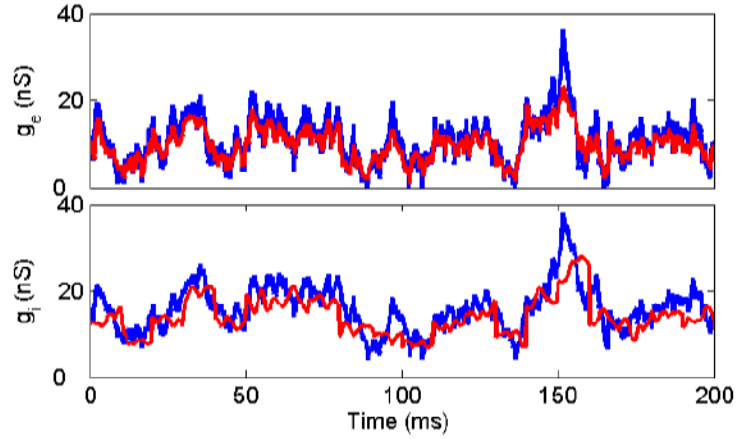

Figure 2 – Estimated conductances (red) vs. actual conductances (blue) in a numerical simulation of a neuron with fluctuating synaptic conductances (including an electrode model)

(3) *Test of the WNI method in vivo.* We will test the WNI method in intracellularly-recorded V1 neurons in vivo. This estimation will be done conjointly with the part (5) of project 2.1.3. and will provide a supplementary estimate of conductance which will be compared with other methods. If the method works, it will be used to perform estimates of single-trial ge and gi conductances in various stimulus configurations, thereby yielding information about the trial-to-trial variability of the respective timing of excitation and inhibition, an information which is presently not possible to estimate. This part will be performed at UNIC, with help from INRIA.

2.3 – Extraction of network correlations from voltage recordings

2.3.1 – Principle

The proposed method consists of two stages. First, from membrane potential recordings of neurons subject to constant current injection (current-clamp), or current recordings in voltage-clamp experiments, information about the mean and variance of total excitatory and inhibitory synaptic conductances can be deduced. Second, the total excitatory and inhibitory synaptic conductances are a direct consequence of the combined activity at thousands of synaptic terminals, and the mean and variance can be linked to the average release rate and correlation (synchrony) among these individual terminals. Combining both stages thus links intracellular activity observed in experiments to statistical properties of the activity of the pool of synapses, and hence the activity in the surrounding neural network. The interest of such a method is considerable, as it could provide for the first time a tool to infer statistical properties of the global network activity based on the sole knowledge of local intracellular recordings. It will allow to detect and investigate the effect of specific network states in vivo, such as highly synchronized or oscillatory states observed in the cortex during natural sleep or active wakefulness.

2.3.2 – Preliminary Results

Preliminary results were obtained on both the experimental and theoretical level. Both stages are formulated mathematically in the case of single-compartment neuron models, and were shown to provide a robust way to infer correlations among thousands of synaptic terminals. The test of the proposed method in experiments is difficult, as currently no control over the statistical properties of thousands of presynaptic terminals exists which is available to us. However, an indirect test of the procedure was achieved by studying the membrane potential response of cortical neurons to stimulation of the brainstem (PPT) in anesthetized cats in vivo. Here, morphological reconstructions together with recordings of intracellular activity allowed us to construct biophysical models with spatially distributed synaptic inputs. The

response of these models to simulated synaptic activity was then used to cross-validate results obtained directly from experimental recordings. A good match was found.

2.3.3 – Project outline

(1) *Theoretical development of methods for extracting correlations.* In this part we will confine and further develop the mathematical framework on which the proposed method is based. In the first stage, the Fokker-Planck formalism will be used to assess analytically the membrane equation subject to effective synaptic conductance noise sources in order to link the membrane potential response to specific effective conductance drives. In the second stage, we will utilize the shot-noise formalism to link statistical properties of the activity at thousands of individual synaptic terminals to that of the resulting effective inhibitory and excitatory conductances. Here, simple single-compartment models and exponential synaptic kinetics will be replaced by spatially-distributed models and more elaborated kinetic models of synaptic transmission, respectively. This research will be conducted mostly at UNIC, with help from INRIA on statistical and stochastic methods.

(2) *Test of these methods using numerical simulations.* In this part we will test the various mathematical frameworks in numerical simulations. Simulation protocols will cover a variety of model complexities, ranging from single-compartmental models to multi-compartmental models with synaptic inputs spatially distributed in dendrites. This will be realized at the UNIC with help from INRIA.

(3) *Applications of the method to analysing intracellular recordings in vitro and in vivo.* We will test the proposed method in vitro using various protocols (current-clamp and voltage-clamp in cortical slice preparations displaying spontaneous active states, dynamic-clamp experiments). Although it is not possible to control the statistical signature at thousands of synapses, morphological reconstructions along with detailed biophysical models based on these data will allow us to cross-validate obtained results by independent methods. The proposed procedure will also be applied to experimental results obtained in the visual cortex of cats in vivo. The research will be conducted at UNIC.

2.4 – Probing conductances with conductance noise injection

2.4.1 – Principle

The principle of this method is to “probe” cortical neurons by injecting conductance noise. The response to conductance noise is a compromise between the injected conductance and the intrinsic conductances present in neurons. Our goal is to obtain methods to deduce qualitative information concerning the type and density of currents present in neurons using this method. The same method can also be used to deduce information about the electrotonic structure of the neuron, which is an essential parameter to understand integrative properties. The interest of this method is that it could be applicable in vivo, which would open the possibility of studying intrinsic conductances in cortical neurons in various conditions or levels of anesthesia.

2.4.2 – Preliminary Results

The only preliminary result we have obtained so far is to switch bursting cells into regular-spiking neurons by using conductance noise injection (not shown). In this case, the injected conductance “competes” with the intrinsic conductances responsible for bursting, and prevents them from generating bursts. We expect that it should be possible to relate the amount and characteristics of the injected conductance to optimally compete with different types of intrinsic conductances.

2.4.3 – Project outline

(1) *Theoretical development of the method.* This method will be developed using computational models and mathematical tools if possible. It will be conducted conjointly by UNIC and INRIA.
(2) *Test of the method by using numeric simulations.* The method will be tested using biophysical models of cortical pyramidal cells, with different distributions of currents in dendrites, and different intrinsic properties (bursting, regular-spiking, etc). In vivo-like background activity will be simulated as well, to test the robustness of the method and its applicability in vivo. This part will be realized by UNIC with help from INRIA.
(3) *Experimental tests of the method.* The method will be first tested in dynamic-clamp in vitro. In this case, the level of background activity is low, and neurons are driven mostly by their intrinsic propeties. The method will also be tested in vivo if its robustness can be demonstrated. This work will be carried out at the UNIC.

2.5 – Spike-triggered averages from voltage recordings

2.5.1 – Principle

The principle is to extract the excitatory and inhibitory conductance variations leading to spikes in central neurons. We will first study the problem theoretically, using the Fokker-Planck formalism. Our goal is to obtain a procedure to extract the conductances from the sole knowledge of the V_m activity of the recorded neuron, which would lead to very useful tools to analyze the respective role and timing of excitation and inhibition in the spike selectivity of cortical neurons.

The problem can be formalized as follows: before the spike, the membrane equation is given by

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_e(t)(V - E_e) - g_i(t)(V - E_i) + I ,$$

where C_m is the specific membrane capacitance, g_L is the resting (leak) conductance, EL is the resting V_m (leak reversal), and g_e, g_i are the excitatory and inhibitory conductances, respectively, with E_e and E_i their respective reversal potentials. The goal of the method is to extract the time course of $g_e(t)$ and $g_i(t)$ preceding spikes in a given neuron. To this end, we use recordings at several levels of DC current injection (I) and will try to solve the equation analytically using reasonable templates for $g_e(t)$ and $g_i(t)$. Another method will be to inject white noise of weak amplitude (to preserve spike initation) and use the WMI method (see above) to estimate the conductance time course preceding spikes (single-trial conductances in this case).

2.5.2 – Preliminary Results

Preliminary results were obtained about the optimal conductance patterns that trigger spikes in cortical neurons. By using dynamic-clamp injection of stochastic conductances, we compared two states, one “low-conductance” (LC) state, where g_e and g_i were of the same overall magnitude and were small compared to the resting conductance (g_L), and one “high-conducance” (HC) state, where both conductances were strong (inhibitory conductances must dominate in this case, to maintain the Vm around –65 mV). We found that the optimal patterns for triggering conductances are an increase of excitation in LC states and a decrease of inhibition (dis-inhibition) in HC states. The latter is interesting, because it is also paralleled with a decrease of the total conductance prior to the spike. This can be shown as a signature of HC states and we hope to be able to identify this signature from in vivo recordings.

Furthermore, the optimal conductance pattern can be fit reasonably well by a single exponential time course. Thus, inserting such time courses in the membrane equation above should lead to a system solvable analytically, which would then lead to a method for extracting ge/gi time courses from the sole knowledge of V_m activity.

2.5.3 – Project outline

(1) *Theoretical development of the method to analyze spike-triggered averages from intracellular recordings.* The framework of both spike-triggered averages of Vm activity, and white noise injection (see above) will be developed theoretically, in collaboration between UNIC and INRIA.
(2) *Numerical test of the method using computational models of various levels of complexity.* We plan to first test the methods using different computational models of neurons: first, a single-compartment model with fluctuating conductances (this model can be implemented in in vitro experiments – see below); second, a single-compartment model receiving more realistic patterns of synaptic inputs; third, a compartmental model of cortical pyramidal neuron, where inputs are located in dendrites. This part of the proposal will provide a quantitative correspondence between the estimated conductance using the method, and the conductance present in the synaptic inputs. This part will be performed at UNIC with the help from INRIA.
(3) *Test of the method in dynamic-clamp.* We will test the method in vitro using controlled conditions where we know exactly what conductance was injected in the cell. The results from the method will be compared to the injected conductance, providing a direct estimate of the reliability and precision of the method. This will be done using both sharp and patch electrode dynamic-clamp, and will be performed by UNIC.
(4) *Applications to intracellular recordings in vivo.* We will analyze existing intracellular recordings in V1 neurons, for both spontaneous activity and responses to visual inputs. We also have a collaboration with Igor Timofeev (Laval University, Canada), to analyze intracellular recordings performed in awake cats. In both cases, we will obtain estimates of the optimal excitatory and inhibitory conductance patterns triggering spikes in these neurons, which is a piece of information presently unavailable in the literature (to our knowledge). Specific experiments will also be designed to inject low-amplitude white noise in V1 neurons. This part of the project will be performed at UNIC.

Justification for man-power and equipment

More than two full-time equivalent of personel already present will be working on the project, and we will need two additional full-time equivalent (one postdoc at UNIC, one postdoc at INRIA) for the whole 3-year period. The UNIC postdoc will do both modeling and experimental work (dynamic-clamp in vitro) and will also assist the in vivo experiments. He/She will also work closely with the INRIA and frequent visits will be necessary. The INRIA postdoc will also directly assist the experiments and design experimental protocols.

We already have two sharp-electrode setups (in vivo and in vitro) at UNIC, and these setups are fully equiped with a dynamic-clamp system. We do not request equipment for this part (except for minor modifications of the dynamic-clamp systems). We also have aquired a patch-clamp setup conjointly with the modeling and experimental groups of UNIC. We need to complete this patch setup with a performant microscope allowing fluorescence (for dendritic patch) as well as equip this setup with the ability to perform dynamic-clamp experiments, which are essential in this project. We also need to acquire sufficient computational means to run the different models presented here (several workstations are needed for the personel hired in the grant, both at INRIA and UNIC). Finally, we request a participation to the costs of animal experiments needed for this project (in vivo and in vitro).

Grant management

Frequent exchanges between INRIA and UNIC will be necessary, and indeed we are already collaborating in a European project since September 2005 (with no overlap with this proposal). Dr. Brette has worked as a postdoc at UNIC before joining the INRIA, so the exchanges between our teams are already frequent. We will organize regular group meetings between UNIC and INRIA, where both mathematicians, computational and experimental biologists will participate. These meetings should identify possible problems and take appropriate actions which will be decided collectively.

References

1. A. Manwani, C. Koch, *Neural Comput* **11**, 1797 (Nov 15, 1999).
2. A. Destexhe, M. Rudolph, D. Pare, *Nat Rev Neurosci* **4**, 739 (2003).
3. M. Steriade, *J neurophysiol* **86**, 1 (2001).
4. V. Braitenberg, A. Schüz, *Cortex: statistics and geometry of neuronal connectivity* (Springer-Verlag, Berlin, 1998), pp.
5. D. Pare, E. Shink, H. Gaudreau, A. Destexhe, E. J. Lang, *J neurophysiol* **79**, 1450 (1998).
6. A. A. Sharp, M. B. O'Neil, L. F. Abbott, E. Marder, *Trends Neurosci* **16**, 389 (1993).
7. H. P. Robinson, N. Kawai, *J Neurosci Methods* **49**, 157 (Sep, 1993).
8. A. Destexhe, M. Rudolph, J. M. Fellous, T. J. Sejnowski, *Neuroscience* **107**, 13 (2001).
9. J. M. Fellous, M. Rudolph, A. Destexhe, T. J. Sejnowski, *Neuroscience* **122**, 811 (2003).
10. F. S. Chance, L. F. Abbott, A. D. Reyes, *Neuron* **35**, 773 (2002).
11. Y. Shu, A. Hasenstaub, M. Badoual, T. Bal, D. A. McCormick, *J neurosci* **23**, 10388 (2003).
12. S. A. Prescott, Y. De Koninck, *Proc natl acad sci u s a* **100**, 2076 (Feb 18, 2003).
13. C. Mehring *et al.*, *Soc. Neurosci. Abstr.* **26**, 828.11 (2000).
14. C. Monier, F. Chavane, P. Baudot, L. J. Graham, Y. Fregnac, *Neuron* **37**, 663 (2003).
15. M. Wehr, A. M. Zador, *Nature* **426**, 442 (2003).
16. W. B. Wilent, D. Contreras, *J neurosci* **25**, 2983 (Mar 16, 2005).
17. W. B. Wilent, D. Contreras, *Nat Neurosci* (Sep 11, 2005).
18. J. Anderson, M. Carandini, D. Ferster, *J neurophysiol* **84**, 909 (2000).
19. M. Rudolph, Z. Piwkowska, M. Badoual, T. Bal, A. Destexhe, *J neurophysiol* **91**, 2884 (Jun, 2004).
20. V. Bringuier, Y. Fregnac, A. Baranyi, D. Debanne, D. E. Shulz, *J physiol* **500 (Pt 3)**, 751 (1997).
21. M. L. Hines, N. T. Carnevale, *Neural Comput* **9**, 1179 (Aug 15, 1997).
22. R. Brette, M. Rudolph, Z. Piwkowska, T. Bal, A. Destexhe, *Soc. Neurosci. Abstracts* **31**, 688.2 (2005).
23. M. Rudolph, Z. Piwkowska, R. Brette, A. Destexhe, T. Bal, *Soc. Neurosci. Abstracts* **31**, 687.13 (2005).
24. O. Faugeras, R. Keriven, *IEEE Transactions on Image Processing* **7**, 336 (1998).
25. O. Faugeras *et al.*, *Neuroimage* **23S1**, S46 (2004).
26. J. Kybic, M. Clerc, T. Abboud, O. Faugeras, *IEEE Transactions on Medical Imaging* **24**, 12 (2005).
27. B. Thirion, O. Faugeras, *Medical Journal Analysis* **8**, 403 (2004).
28. O. Faugeras, G. Hermosillo, *Siam Journal of Applied Mathematics* **64**, 1550 (2004).

Signature du coordonnateur scientifique
pour la version papier à renvoyer à l'Inserm :