Single cell and population activities in the olfactory bulb and the hippocampus

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Synopsis

Dynamics of single cells and large cell populations are the subject of investigation by using differently detailed models. Multicompartamental modeling techniques are used to systematically investigate the location-dependent effects of GABA-ergic dendritic inhibition on the firing patterns of pyramidal cell. The appearance of stochastic resonance in the model of mitral and granule cells of the olfactory bulb is demonstrated by using single-compartmental model approach. Spatial propagation of synchronized activities in hippocampus slices are studied by a model of large neural populations.

1 Introduction

1.1 Neural modeling: multiple strategies

Structure-based bottom-up modeling has two extreme alternatives, namely multi-compartmental simulations, and simulation of networks composed of simple elements. There is an obvious trade-off between these two modeling strategies. The first method is appropriate to describe the activity patterns of single cells, small and moderately large networks based on data on detailed morphology and kinetics of voltage- and ligand-dependent ion channels. The second offers a computationally efficient method for simulating large networks of neurons where the details of single cell properties are neglected. As a compromise between the two extreme approach, the behavior of large networks of neurons may be studied by population theories /54,28,8/.

In our studies specifically, the investigated neural centers are the olfactory bulb (OB) and the hippocampus. The olfactory bulb and the hippocampus are both neural structures that are closely connected to the cortex. Though the delimitation of the (neo)cortex from its neighbours has been suggested to be quantitative rather than qualitative /12/, both the OB and the hippocampus are considered in some extent as cortical-like struc-
tures. The hippocampus itself participates in processing olfactory information and the OB projects (albeit sparsely) to the entorhinal cortex as well. Both the hippocampus and the olfactory system exhibit complex dynamic behavior: they generate rhythmic temporal patterns with different frequencies and with variable spatial coherence. Both systems were suggested to be candidates for chaos generators, too. Global electric patterns measured by EEG have behavioral correlates, and have crucial roles in learning and memory formation. For some comparison of the olfactory system with the hippocampus, see Arbib et al /7/.

In the present paper we briefly show two applications of compartmental modeling and one of the theory of neural populations. Our main aim is to illustrate that understanding neural phenomena occurring at different hierarchical levels and spatiotemporal scales requires different type of modeling strategies and tools. First, the distinction between somatic and dendritic inhibition for hippocampal pyramidal cells is studied. Here we use very detailed *multicompartmental* model, and effects due to relatively small differences in the location are demonstrated. Second, we study the question whether or not stochastic resonance may be a candidate for being a mechanism of amplifying weak signals during odour information processing. Since we were interested in the interplay of a nonlinear system with an external periodic signal subject also to noise, we used again the Hodgkin-Huxley scenario. We concentrated to the mechanism of the amplification of the weak external signal, and therefore nonlinear models of the neurons had to be defined. We used *single-compartmental* models reduced from multicompartmental models. Single compartmental models proved to be efficient compromise between the less realistic integrate-and-fire model and the computationally more time-demanding multicompartmental models. Third, the emergence and propagation of synchronized *population* activity in the hippocampal CA3 region is examined. We developed a new theoretical method and a computational model to simulate neural population phenomena /8,28/. Having been motivated by Ventriglia’s /52-54/ assumptions we treat statistically
the interaction between neural and spike populations. To be able to make large-scale simulations many structural details have to be sacrificed. This loss is compensated by incorporating into the population mode a relatively detailed single cell model. This model is capable to reflect the basic firing patterns of a hippocampal pyramidal cell including its capability to exhibit bursting behaviour.

2 Effects of location of inhibition on hippocampal pyramidal cells

2.1 Location-dependent inhibition of the pyramidal cells

Inhibitory synapses are thought to be distributed throughout the dendrites and the soma of pyramidal cells in several cortical regions. Recent experimental evidence suggests that inhibitory synapses of different locations are associated with specific actions based on their position. It has been observed that IPSP responses to GABA have different time-courses corresponding to the different locations of receptors. This can be explained by either the electrotonic filtering by the dendritic tree or different subspecies of GABA_A receptors giving rise to distinct responses. Pearce /41/ has found that these differences are explained by different ratios of two pharmacologically distinct species of GABA_A receptors in the dendrites versus the soma. In paired recordings conducted by Miles and coworkers /39/, where response properties could be directly related to specific synapses, IPSPs could be fitted with single exponentials which raises the possibility that the differences are due to filtering effects. This is interesting because if different IPSPs are due to post-synaptic receptors with identical kinetics, then it is curious how the different actions attributed to these synapses arise.

2.2 Methods

We have used the standard multi-compartmental biophysical modeling technique with the GENESIS simulator. We simulated a passive pyramidal cell both with simplified "ball
& stick” and with detailed morphology based on Traub et al. /50/. The synapses were modeled with double exponential kinetics.

\[
G_{syn} = \frac{G_{max}}{\tau_2 - \tau_1} \left( e^{\frac{t}{\tau_2}} - e^{\frac{t}{\tau_1}} \right) \quad \text{for} \quad \tau_2 > \tau_1
\]  

We explored the parameter space to get a good fit for IPSPs as measured experimentally by Miles et al. /39/. For each run we found the values of time-to-peak, amplitude and duration-at-half-amplitude for the simulated IPSPs and by comparing them with the values of the measured ones calculated the error.

### 2.3 Results

First, we tried to reproduce the somatic IPSP measured in /39/ by finding the optimal values for the parameters of our synaptic conductance kinetics. In this case we modeled applying inhibition to the soma and, as throughout our whole work, recording the changes of membrane potential in the somatic compartment. We made a detailed exploration of the parameter space and in the following simulations we used the parameters and parameter intervals found to be best for reproducing the measured averages and standard deviations resp. of the three characteristic properties (time to peak, amplitude and duration at half amplitude) of somatic IPSPs.

We then started to change the location of inhibition, but not the parameters of the synaptic kinetics, by applying it to different dendritic compartments, each time further from the soma. We recorded the membrane potential at the soma and examined the change in parameters of the IPSP and the total error of the fit with respect to the dendritic IPSP measured in /39/. There was an optimal electrotonic distance needed for reproducing the average dendritic IPSP that translated into an anatomical distance of 250-500 micron. Deviation of dendritic IPSPs was also successfully reproduced by changing the parameters only in the intervals found previously.
Our simulations showed that it is possible to reproduce the differences seen between somatic and dendritic IPSP as measured at the soma (Fig. 6), thus raising the possibility that although there are a number of known GABA$_A$ receptors, interneuron to pyramidal cell synapses use the same one regardless of location. This is supported by our simulation of the electrotonic attenuation with morphological distances comparable to that seen in reconstructed cells. Future simulations can describe the functional effects of this electrotonic attenuation of IPSPs on the bursting behavior of pyramidal cells.

While trying to make variations in IPSPs by changing the kinetic parameters of the synapse we were faced with the (not contraintuitive) fact that at least two properties of PSPs (time to peak and duration at half amplitude) did not vary independently, indeed there was a pronounced linear relationship between them. This gives a hint that the properties most commonly used to characterize PSPs by electrophysiologists are at least redundant and probably not appropriately chosen. Further investigations could enlighten the possible consequences of this linearity and also the parameters it depends on.

3 Stochastic resonance in the cells of the olfactory bulb

3.1 Stochastic resonance and its role in neural systems

Eversince its discovery /9,10/, stochastic resonance (SR) became a widely studied phenomenon. Stochastic resonance is a mechanism, where noise plays a beneficial role in amplifying weak periodic signals arriving to some nonlinear system.

The SR phenomenon can be described specifically for systems characterized by binary output. Let us consider a simple measuring device/sensor which has two possible outputs 0 and 1, and suppose that the sensor has a sensitivity threshold. If the input signal is below the threshold value, the output is 0, if it is greater or equal to it, the output is 1.
If the input signal is periodical, with its maximum below the threshold, the sensor will detect nothing. By adding some noise to this signal there is a nonzero probability that signal+noise may overcome the threshold value, and the detector will sense the signal. The signal to noise ratio as a function of noise may show a maximum, i.e. there is a certain noise level which characterizes the performance. Too small noise is not sufficient to make the signal detectable, while too large noise suppress the information content of the signal.

The SR phenomenon is much more general than in the previous oversimplified examples. Several different generic theoretical models for the occurrence of SR exist. Though the phenomenon first was found in bistable system, later it was also demonstrated in monostable, excitable systems. Neurons are prototypes of this latter class.

SR was found both experimentally and by model studies in various neurons and neural ensembles. Douglass et al 1993 showed that the mechanoreceptor hair cells of the crayfish shows SR, while Levin and Miller 1996 demonstrated SR on the cercal system of the crickets. Collins et al 1996 demonstrated SR in experiments on mammalian cutaneous mechanoreceptors. Both experimental (Braun et al) and modeling (Longtin Hinzer 1996) studies of temperature receptors have concluded that the interplay of subthreshold oscillation and noise imply the generation of the firing patterns. The presence of noise can enhance transmission of spike trains, /25/ and a transmission capacity /15/. The possible role of SR in neural coding is discussed in /17,13/.

The interpretation of the models can differ whether the origin of noise is intrinsic, i.e. we assume that neurons are stochastic units, or that the origin of noise is extrinsic, i.e. we allow the neurons to be deterministic input-output units which receive stochastic inputs. (Of course, we can allow the noise being originated from both sources). In neural modelling noise is used to alter the behaviour of deterministic neural equations, and its
beneficial role suggests a possible biological significance in understanding the realistic biological behaviour.

Noise can enhance the neuron’s sensitivity. Consider a deterministic receptor neuron in the olfactory system devoid of random spontaneous activity; it fires an action potential when the receptor potential and consequently the odorant concentration exceeds a certain threshold. This means that any odorant concentration smaller than this threshold cannot be signaled to the brain. Consider now a "stochastic neuron" where the receptor potential presents a random (thermal) component added to the deterministic component that results from odorant stimulation. The presence of noise produces a finite probability for the signal+noise to be greater than the threshold value, and the cell activity may result in firing. Consequently, the neuron sensitivity at low concentration is greater than without noise /51,56,34/.

Stochastic resonance in networks differs from SR in units, because the presence of noise does not degrade significantly the detection of suprathreshold signals /18/. One unexpected result obtained is that the capacity of a system (neuron or neural network) to extract signal from noise is independent of noise intensity, provided a minimal intensity is exceeded and the elements are uncoupled. So, there is no need for adjusting the noise intensity to some optimal level. However, when the elements (e.g. ion channels or neurons) are coupled the existence of an optimal noise and an optimal coupling have been suggested /31/.

In future modelling the origin of noise will probably be related to statistical description of more detailed model of synaptic junctions and ion channels, and collective behaviour of large neural assemblies.
3.2 Modeling mitral and granule cells

The olfactory bulb is the first relay center of the olfactory system. The generation and propagation of action potentials in the two major cell types of the olfactory bulb, i.e. in the mitral and granule cells, have been earlier simulated by applying the multi-compartmental modeling technique.

By using the traditional deterministic framework four types of problems have been studied related to the signal generation and propagation in the OB. /5,6/.

(i) The effects of the individual currents and their role in the generation and suppression of action potentials, and in the control of firing frequencies (intra-compartmental studies).
(ii) Signal propagation through the compartments of both the mitral and granule cells have been simulated. The effects of both orthodromic and antidromic stimulation have been demonstrated.
(iii) The excitatory-inhibitory coupling between the mitral and granule cells through dendro-dendritic synapses and the effects of the (partial) blockade of the GABAergic inhibition have been shown.
(iv) Dynamic behavior of a skeleton network of the bulbar circuitry taking into account even the periglomerular cells has been studied.

3.3 Results

Our own numerical simulation of the stochastic resonance phenomenon was performed on two cell types in the olfactory system: the response of mitral and granular cells were studied to periodic inputs superimposed some noise term by using single compartmental model. The single cell models were based on earlier works, such as /11,5,6/.

On both cells an under-threshold stimulation (20pA mitral and 90 pA granular respectively) sinusoidal (20Hz) current injection was applied superimposed by an additive Gaussian white-noise term with short correlation time ($\tau = 0.1$ ms).
The output power spectrum has been determined by using Fast Fourier Transformation (FFT) from the simulated membrane potential as a function of time, for different input noise intensity. Then the signal-to-noise ratio (S/N) as a function of noise was calculated. The signal was measured by the peak of spectrum at 20Hz and the noise intensity was figured out by averaging in tight frequency bands around 20Hz (16.5-19.5Hz; 20.5 - 22.5Hz). Fig. 1 and 2 shows the output power spectra (1a, 2a) and the S/N curves derived from the Fourier spectra of the membrane potential (1b, 2b) of mitral and granule cells, respectively.

There is no optimum noise level which is possibly due to the fact that phase shift of the spikes are bad comparing to the sinusoidal membrane potential changes. If we consider, however, the output signals as the series of binary 0 – 1 elements, and FFT is used to calculate the S/N as a function of noise, the results are qualitatively different. Fig. 3a and 4a shows the Fourier spectra of the binary series for the mitral and granule cells, while Fig. 3b and 4b show the calculated S/N – noise intensity curves.

As it was pointed out /Wiesenfeld and Jaramillo 1998/, in biological context information transmission is more significant than SR, and we may ask the follofing question: 'What is the most appropriate measure of of ”output performance?” In this respekt we may say that the binary character of the neurons is the main feature of the performance of the neurons.

The calculations showed optimum noise level for both cell types, so the possibility of the existence of SR phenomenon has been demonstrated. The error limitation drawn on the simulation S/N data has been determined from the uncertainty of noise intensity, which itself was figured out by slight changes on the averaging band limits (16.5-19.5Hz → 16-19Hz; 20.5-22.5Hz → 21-23Hz). The big fluctuation of the resonance peak curves, however, cannot be explained by this estimation method. More precise error estimation
should be done by making the simulations using a different random variable generator. Neurons are often analysed by interspike intervall histograms (ISIH). These histograms show a peak at the reciprocal value of the mean firing rate (MFR) corresponding to the characteristic frequency (spectrum). On Fig. 5a and 5b there are such histograms pertaining to mitral and granular cells. These figures are obviously only illustrations; the simulations performed by one of us /57/ were too short in run time to obtain definite conclusions. However, it can be recognised from these figures that peaks at the driving frequency due to the noise arise.

Reliable numerical simulations in case of additive noise (i.e. to generate realization of stochastic processes) need careful consideration, and here we cannot go into the technical details. Usually one has to choose shorter integration step than the characteristic time of the fastest events in the model with reasonable running time. In these cases the time step was 0.01 ms and the characteristic time of the fastest event (i.e., the noise) was 0.1 ms long. As the noise was deterministic, given independently on the cells states, the implicit integration methods remain rather stable and reliable. All simulations were performed with the NEURON program package using the second order Crank-Nicholson integration scheme during 20957.0 ms long time interval.

4 A Statistical Approach to Neural Population Dynamics

4.1 Statistical approach to the generation and propagation of hippocampal synchronized activity

There is a long tradition to try to connect the ‘microscopic’ single cell behavior to the global ‘macrostate’ of the nervous system, analogously to the procedures applied in statistical physics. Global brain dynamics is handled by using continuous (neural field) description instead of the networks of discrete nerve cells. Both deterministic, field-theoretic /27,45,55,3/ and more statistical approaches /2,42/ have been developed. Here we briefly
present the framework of a model for being able to describe synchronized population brain activities and wave propagation in large neural systems, such as cortical structures.

4.2 Basic model properties

The description of population activity of neurons requires different mathematical apparatus from that of individual neurons. In addition, the statistical approach presented here uses the notion of two separate populations, one for the neurons and the other for action potentials. Thus, for the sake of simplicity, the following expressions will be used throughout the rest of the paper:

- **spike emission**: action potential generation
- **number of emitted spikes**: number of synaptic sites that a single action potential can reach
- **spike propagation**: action potential conduction through the axonal arbor
- **spike absorption**: arrival of the action potential at a synaptic site and change of postsynaptic membrane conductance
- **probability density function**: refers to the number of neurons/spikes that are in a given state at the same time
- **diffusion**: the effects, not explicit in the model, that make the neurons/spikes get to slightly different states

The model describes neural population activity in terms of the probability density functions (p.d.f.’s) of (i) neurons and (ii) spikes travelling between the neurons. This idea is adopted from earlier work by Ventriglia /52, 53, 54/. The state space consists of the two-dimensional space coordinate \( r \) (for both neurons and spikes), a membrane potential coordinate \( u \) (for neurons), and an intracellular calcium-concentration coordinate \( \chi \) (for
pyramidal neurons only). The different neural populations (pyramidal and two types of inhibitory cells) have their own neuronal fields which can interact through the emission and absorption of spikes (action potentials). The neurons are fixed in space while spikes can travel among them. Two diffusion processes are defined. The first describes the diffusion of the state of a single cell in the two-dimensional state space, the second corresponds to the evolution of the probability densities in the two-dimensional plane. The model is fully specified elsewhere 
while the general population equations can be found in the Appendix.

4.3 Results

In previous studies population activities as well as underlying single cell voltages were simulated during normal and epileptiform activities in the hippocampal CA3 slice.

The role of inhibitory and excitatory interactions is studied in the simulations presented here. A range of epileptiform and non-epileptic rhythms has been obtained. For classification of these behaviors, the measure of synchronization is defined as the percentage of simultaneously (within 3ms) firing pyramidal cells. The underlying single cell activities can be studied by collecting the values of synaptic inputs from the simulation of the population model and then running the single cell model using this data “average synaptic input” of the subpopulation containing the given cell. Thus the model also offers the possibility to follow the activity of an ‘average cell’ at any point of continuum.

The composite figure shows a set of phenomena, such as fully synchronized population burst, synchronized synaptic potentials and low amplitude population oscillation. ** Fig. nn. osszerakott !! **
4.4 Wave propagation

The dynamics of activity propagation in cortical, thalamic and hippocampal system has been recently studied both experimentally and by simulation methods /38,49,19,26,16/ In totally disinhibited slices the velocity of propagation in longitudinal slices was found about 15 cm/s in the hippocampus.

The spatial pattern of propagation is shown in Fig. 7. The model slice is shown with increasing time from top to bottom. High activity first appears in the stimulated subregion, then builds up in the neighboring regions, and then propagates through the full length of the slice. The velocity of the simulated wave propagation exhibits a linear increase on the maximal synaptic conductance, and it is in the interval $5 - 10 \text{cm/s}$. The velocity of activity propagation was investigated as a function of the maximal conductance of excitatory synapses (Fig. 8).

The dependence of velocity of the wavefronts on the synaptic parameters is a hot issue. Chen et al. /16/ derived a power-law relationship between the velocity and the maximal synaptic conductance. Golomb and Amitai /26/ found that in a large parameter region the velocity is a linearly increasing function of the maximal synaptic conductance, at least above some thresholds. ** meg meg a Nat. Neur-ban talat is. **

5 Discussion

Computational neuroscience and neurodynamic system theory is pluralistic /7/. Neither the reductionistic research strategy which adopts biophysically detailed cell models nor the statistical treatment of large population of simplified elements can be qualified as the 'only' useful technique of neural modelling. We illustrated the power of compartmental modelling (i) in taking into account fine geometrical details, (ii) signal generation and amplification in single cells; while the kinetic model has been proven a proper tool for studying synchronization and propagation effects in large neuron populations.
6 Appendix

6.1 The General Population Equations

For the population behavior, a diffusion model is defined which enables cells that are initially in the same state to be dispersed among different states. Two kinds of diffusion processes are taken into account: the temporal evolution of the p.d.f-s of the neurons is a diffusion process in the state space of the single cell, while the p.d.f-s for the spikes is a diffusion in the real space.

The single cell module should be set up based on different ionic conductances specific to each cell type. The model we defined for hippocampal pyramidal cell explicitly describes the interspike dynamics by using membrane potential and calcium concentration as variables, and specifies the firing probability. Soft firing threshold is realized by voltage-dependent firing probability. For each specific problem a single cell model should and could be defined.

Absorbed spikes induce time-dependent post-synaptic conductance change, expressed by the $\alpha$-function. To shorten the forthcoming expressions we denote $(r, u, \chi, t)$ as $X$, and $(u, \chi, t)$ as $Y$.

\[
\frac{\partial g_s(X)}{\partial t} + \frac{\partial}{\partial u} (\varepsilon_s(X) g_s(X)) + \frac{\partial}{\partial \chi} (\eta_s(u, \chi) g_s(X)) \\
- \frac{D_u}{2} \frac{\partial^2 g_s(X)}{\partial u^2} - \frac{D_\chi}{2} \frac{\partial^2 g_s(X)}{\partial \chi^2} = b_s(X) - n_s(X)
\]  

where $\varepsilon_s$ and $\eta_s$ describe the electric current and the calcium influx to the cell, respectively, to be specified by the actual single cell model. The function $n_s$ is the p.d.f. expressing the rate at which neurons are starting to fire, and $b_s$ is the same for neurons returning from firing:

\[
n_s(X) = \begin{cases} 
  p_s(u)\varepsilon_s(X)g_s(X) & \text{if } \varepsilon_s(X) > 0 \\
  0 & \text{otherwise}
\end{cases}
\]
\( p_s(u) \) being related to the voltage dependent firing probability, and

\[
b_s(X) = \int dY' n_s(r, Y') \delta(u - U_s(Y')) \delta(\chi - \chi_s(Y')) \delta(t - T_s(Y'))
\]

where \( \int dY' \) stays for \( \int_{-\infty}^{t} dt' \int_{-\infty}^{\infty} du' \int_{0}^{\infty} d\chi' \), the functions \( U_s, \chi_s, \) and \( T_s \) contain the firing mechanism, telling when and at which point of the state space firing should end. Eq. (4) ensures that the number of neurons is preserved, i.e. after sufficiently long time all neurons return from firing.

\[
\frac{\partial f_{s}^{\alpha}(r, t)}{\partial t} + (v_{s}^{\alpha} \nabla) f_{s}^{\alpha}(r, t) - \frac{D_{r}}{2} \nabla^{2} f_{s}^{\alpha}(r, t) = -\sigma_{s} f_{s}^{\alpha}(r, t) + \lambda_{s}^{\alpha} \int_{-\infty}^{\infty} du' \int_{0}^{\infty} d\chi' n_{s}(r, Y')
\]

where \( v^\alpha \) is the velocity of spikes in direction \( \alpha \), \( \sigma \) and \( \lambda^\alpha \) are the absorption and emission coefficients, respectively. The previous model is introduced and discussed in detail in Refs. /8,28/

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