34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Modeling the Influences of Nanoparticles on Neural Field Oscillations in Thalamocortical Networks

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***Abstract*—The purpose of this study is twofold. First, we present a simplified multiscale modeling approach integrating activity on the scale of ionic channels into the spatiotemporal scale of neural field potentials: Resting upon a Hodgkin-Huxley based single cell model we introduced a neuronal feedback circuit based on the Llinás-model of thalamocortical activity and binding, where all cell specific intrinsic properties were adopted from patch-clamp measurements. In this paper, we expand this existing model by integrating the output to the spatiotemporal scale of field potentials. Those are supposed to originate from the parallel activity of a variety of synchronized thalamocortical columns at the quasi-microscopic level, where the involved neurons are gathered together in units. Second and more important, we study the possible effects of nanoparticles (NPs) that are supposed to interact with thalamic cells of our network model. In two preliminary studies we demonstrated *in vitro* and *in vivo* effects of NPs on the ionic channels of single neurons and thereafter on neuronal feedback circuits. By means of our new model we assumed now NPs induced changes on the ionic currents of the involved thalamic neurons. Here we found extensive diversified pattern formations of neural field potentials when comparing to the modeled activity without neuromodulating NPs addition. This model provides predictions about the influences of NPs on spatiotemporal neural field oscillations in thalamocortical networks. These predictions can be validated by high spatiotemporal resolution electrophysiological measurements like voltage sensitive dyes and multiarray recordings.**

I. INTRODUCTION

The branch of modern nanomedicine comprises an ever increasing field of nanoparticles (NPs) applications. Since NPs have the potential to move barrier-free through organic membranes, the consideration of NPs utilized in drug delivery systems is very promising. Based on this our research goal is to study NPs-neuron-interactions at different spatiotemporal scales. Many interesting questions in terms of possible influences on neuronal processes and mechanisms are not directly to observe. Reasons are, e.g., the complex neuronal interactions cannot be investigated in vitro, in vivo measurements are not possible since the measuring points cannot be reached without damage or the spatiotemporal scale does not allow for direct measurements. For these reasons, models are essential in neuroscience: questions about neuronal function are generally addressed by inference on models that link to neuronal processes that are hidden from direct observation. In a preliminary study we examined the effects of silver-NPs imbedded in an organic coating (Ag-NPs) on neuronal cells via patch-clamp measurements and mapped the observations to a single-cell model to investigate and describe the underlying mechanisms [1]. Based on this we studied the impact of those NPs on the signalling behavior of neuronal feedback circuits [2]. For this purpose we built a new computational model on the spatiotemporal scale of small networks that rests upon the idea of corticothalamic interaction and binding introduced by Llinás et al. (see [2] and reference within). After modeling the circuit's thalamic neurons exposed to Ag-NPs, we found NPs induced differences on the firing patterns of all evolved neurons.

In the present study, our first purpose is to extend the referred model of thalamocortical interaction by incorporating a model that gives information about the local neural field phenomena. These fields are evoked on an extremely small and very local cortical area due to the synchronized activity of such parallel thalamocortical functional columns. Second, we utilize this new multiscale model to examine if the NPs' neuromodulatory effects in [2] can also be observed within the spatiotemporal scale of the resulting and much more blurred neural field potential. For this first and basic approach, a one-dimensional Amari neural field model [3] with the extension of an inhibitory layer was developed. The firing patterns of pyramidal dendritic and somatic compartments were transferred to serve as input for the field model.

II. METHODS

A. Model of Thalamocortical Interactions

In the 1990s, Llinás and his colleagues performed a sequence of sophisticated studies on thalamocortical interactions. Based on this data, they developed a detailed model on the microscopic scale that is able to integrate the information from conscious states and that coevally addresses the binding problem, i.e., binding input from different sensory modalities (see [2] and references within). In their measurements, Llinás and his group observed phased oscillations running from the anterior to the posterior part of the cortex about 40 times per second. In their model the interaction is based on two families of oscillators: the specific resonant loop containing specific thalamic cells (STC) that project to the corresponding distinctive cortical areas and help to bind the various attributes of a single event while the non-specific resonant loop comprises intralaminar non-specific thalamic cells (NSTC) that project in a more dispersed way across larger areas of the neocortex [4]. Fig.1 depicts these two thalamocortical resonant loops as used in our study. Llinás et al. propose that neither of the two systems alone can generate cognition. Consistent with this

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model, damage to the specific system arouses loss of particular modality while damage to the non-specific system produces deep disturbances of consciousness [5]. Neuronal assemblies that pertain to a designated piece of conscious content are those that oscillate phase locked not only with one another, i.e. binding numerous attributes of that content together, but also with the non-specific gamma-band oscillations along the dendritic trees of pyramidal neurons (PY) over broader areas of the cortex [5, 6]. Compendious, the system operates on the

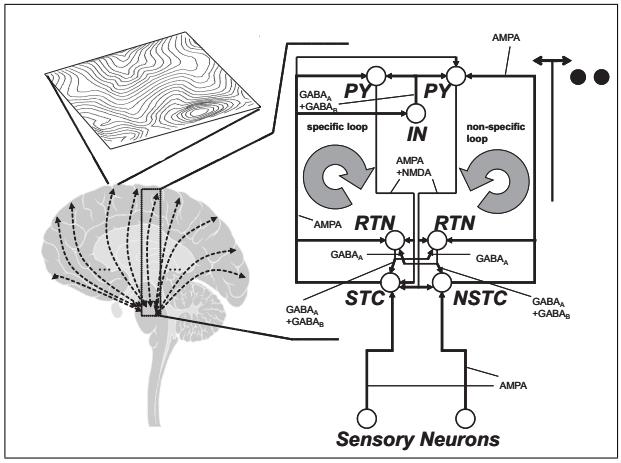

Fig. 1. Simplified thalamocortical model based on the idea of Llinás et al. [5] comprising a description of the synaptic interconnections.

basis of thalamocortical resonant columns that provide global cognitive experiences: in this context, the specific system provides the content that relates to the cognitive task while the non-specific system would engender the temporal conjunction, i.e., the synchronized binding circuit. Our developed simplified *in silico* model is based on this idea. The applied circuit rests upon kinetic models of thalamic cells (TC) including specific thalamic cells (STC), non-specific thalamic cells (NSTC) and reticular thalamic neurons (RTN), as well as inhibitory cortical interneurons (IN) and pyramidal neurons (PY), where PY were designed as two-compartment models. Every single cell of the simplified thalamocortical model receives various synaptic inputs which are modeled as the sum over all synaptic currents that each cell receives. All single nodes are represented by coupled differential equations according to an extended Hodgkin-Huxley-type scheme. Fig.1 shows the circuitry of the involved neurons. Please follow [2] for a detailed description of the applied model. Although this is a highly simplified representation of the thalamic projections to a two-layered (inhibitory & excitatory) neocortex, there was no additional complexity required for our purposes.

B. The Amari Neural Field Model

Down to the present day the large number of synapses and neurons in a small patch of the cortex is a limiting factor for computational modeling issues. A basic approach how this problem can be processed is selecting a continuum limit and study neuronal circuits in which space is continuous and the macroscopic state variables are mean firing rates [7]. The first effort in modeling activities related to a large amount of neurons was undertaken in [8]. This early approach was just considering one excitatory layer of one type of neurons. Later on, the model in [9] introduced inhibitory synapses that reduce activity by hyperpolarization of postsynaptic neurons. Based on [8], a time-constant for refractoryness as well as rectangular functions that differed in sign to model excitatory and inhibitory postsynaptic potentials was introduced in [10, 11]. It was Amari in the 1977 [3] who studied the mechanism of formation and interaction of non-homogeneous patterns in neural fields under natural assumptions on the connectivity and firing rate function. He introduced an integrodifferential equation that is conform with the dynamics of cortical sources considering spatial and temporal aspects. The Amari model allows for local excitation and distal inhibition which was found to be an effective model for a mixed population of interacting inhibitory and excitatory neurons with typical connections (Mexican hat connectivity) [3, 7, 12]. In recent years, within the increase of computational power, there has been a growing interest in neuronal field models that also beared a variety of extensions for the basic Amari model. Those were for instance the inclusion of multiple populations, spike frequency adaption, neuromodulation, slow ionic currents, etc. [7, 12, 13, 14, 15, 16].

We applied the basic Amari model, extended by a secondary inhibitory layer for first time coupling the Llinás model of thalamocortical interaction to a model representing the corresponding neural field potentials. Regarding a one-dimensional representation of a scalar field $u(x,t)$, where x lies within an interval, the chosen Amari neural field model [3] is expressed as one-dimensional two layer version by

$$\begin{aligned}\tau\frac{du(x,t)}{dt} =& -u(x,t) + h_u + S(x,t) \\ &+ \int w_u(x-x')f[u(x',t)]dx' \\ &- \int w_v(x-x')f[v(x',t)]dx'\end{aligned} \tag{1}$$

where $\frac{du(x,t)}{dt}$ is the rate of each neuron's change of activation level across the spatial dimension x as a function of time t. τ is defined as the time scale of the dynamics and $S(x,t)$ as input. The current activation in the field $-u(x,t)$ at each position x is the first factor that advances the rate of change of activation and due to its negative term, the activation changes towards the activation level h_u, that is relevant for the threshold function f [15]. The local field activation is influenced by the local excitation defined by $\int w_u(x-x')f[u(x',t)]dx'$ and by a lateral inhibition interaction profile v, represented by $\int w_v(x-x')f[v(x',t)]dx'$. The intrafield interaction takes the shape of a convolution over the thresholded field $f(u)$ with a homogeneous convolution kernel w_u. The interfield interaction follows the same scheme with the thresholded field $f(v)$ and convolution kernel w_v. The threshold function can either be a

step function or have a smoother sigmoidal pattern such as

$$f(u) = \frac{1}{1 + exp[-\beta(u - u_0)]}. \quad (2)$$

The sigmoidal function's slope β characterizes the steepness and u_0 the position of the nonlinear function's inflection point. In both cases only the field parts that are sufficiently activated are contributing to intrafield interactions. Moreover, the intrafield interaction shows excitatory behavior over small distances, inhibitory over medium distances and either inhibitory or zero over larger distances (global inhibition). This interaction mode is widely applied in modeling and is often referred to as lateral inhibition [15]. The projections are determined as the convolution of a Gaussian kernel

$$w(x - x') = exp[-0.5\frac{(x - x')^2}{\sigma^2}] \quad (3)$$

with σ determining the width of the excitatory part of the kernel. Please see [3, 15] for a detailed discussion of the applied algorithm.

C. Linking Neuronal Feedback Circuits to Neural Field Dynamics

In [1] we identified the effects of coated Ag-NPs on neuronal cells *in vitro* and were able to map those to an *in silico* model. Based on the achievements of this first model we took a step in the spatial scale and evaluated the influence of NPs on the signalling within the neuronal feedback circuit of thalamocortical interaction [2]. This circuit subserves now as fundament to study the resulting field potentials that emerge from the dentritic and axonal activities during the thalamocortical interactions within this network.

Since there is a strong vertical coupling in the chosen model, it is possible to treat a very small cortical patch as an effective one dimensional configuration. The resulting field area that reflects the network's activity is located within an extremely limited local domain. In [17] the spatial spread of field potentials in comparison to well-localized indices of neuronal ensemble activity, current source density and multiunit activity was investigated . It was found that local field potentials represent very local neuronal processes that exhibit a far larger spatial spread (beyond $200 - 400\mu m$) than that predicted by other reports on this topic [17]. More than one of the described vertical circuits are involved in a thalamocortical interaction process such as the temporal binding to a stimulus. Therefore it is presumed that the spatial neocortex activation within a small patch of stimulus specific neurons, comparable to the mapping in sensory cortices, are found to be temporally synchronized and exhibiting a local field potential pattern [18, 19]. The non-specific thalamic neurons within the network are known to project to broader cortical areas, what also facilitates the spatial distribution of the circuit's activity on a small cortical patch. In our Hodgkin-Huxley like model, the PY neurons are separated into a dentritic and a somatic compartment. The oscillating activity of both, the dendritic tree's characteristic low-pass activity and also the somatic spiking activity were applied to built a gaussian spatiotemporal signal distribution that served as mean firing rate inputs to the neural field model. According to Eq.1, our utilized neural field model is consisting of a two-layer architecture: here, the excitatory (top) layer is representing the mean firing rate of the two-compartments of PY neurons, and the inhibitory (sub) layer is substituting IN neurons, located over a wider spatial area possessing unspecific all-to-all connections (lateral inhibition). We considered a high interaction strength within the neurons in the excitatory layer as well as between excitatory and inhibitory layer neurons. The interaction strength from inhibitory to the excitatory layer was adopted to be a bit weaker.

Applying now this multiscale model (combined network and field model) to study the impact of Ag-NPs may have the potential to give also information about possible effects on localized field potentials. In this model, we assume that only the thalamic neurons, i.e., STC, NSTC & RTN are exposed to NPs. In [2] we presented that NPs, exposed to few cells of neuronal feedback circuits, are acting as neuromodulators and hence are influencing the whole system's signalling behavior. However, the observed differences in firing patterns were less pronounced in the feedback network than those found on the single-cell scale in [1]. Since the circuit's spiking activity is resolved to a distribution function describing the former activity's probabilistic evolution in the neural field model, the question is now if it is still possible to observe a NPs induced effect on the more macroscopic scale of field potentials that spread across a small patch of cortical surface.

III. Results and Discussion

Giving an initial action potential ($4\mu A/cm^2$) to the left sensory neuron (Fig.1), STC depolarizes and the thalamocortical circuit's neurons start oscillating. Instead of the synchronized 40Hz oscillations, we evoked a likewise synchronized 7-8Hz bursting activity to easier identify and compare the model output on a larger temporal scale. The corticothalamic feedback circuit's field activity was simulated for t=2s (=2000 time steps in the model), resulting in smooth dynamic changes in u. Dependent on the spatial and temporal pattern of the field u, the inhibitory layer of IN neurons demonstrates analog field activity v. Fig.2d illustrates the activity for the field u (black line) and the field v (gray dashed line) for an example point in time. After successfully simulating the cortical field potentials emerging from a small cortical patch of synchronized Llinás-model based thalamocortical interactions, we examined if we can also observe effects in those field potentials engendered by NPs. Therefore, we considered the presence of Ag-NPs in the referred thalamic neurons (see [2] for the modeling technique) and simulated again the resulting field activity for t=2s. If the small modifications in the single neuron models (STC, NSTC &RTN) actually result in modified cortical field potentials will be evinced by comparison of the two excitatory field activity recordings. To do so, we calculated the difference matrix of the two field activities as function of time. We could detect a difference potential (Δu) for every time step in the simulation. Fig.2a-c) illustrates this neural field potential difference for three representative points in time in 1D. Further Fig.3 depicts

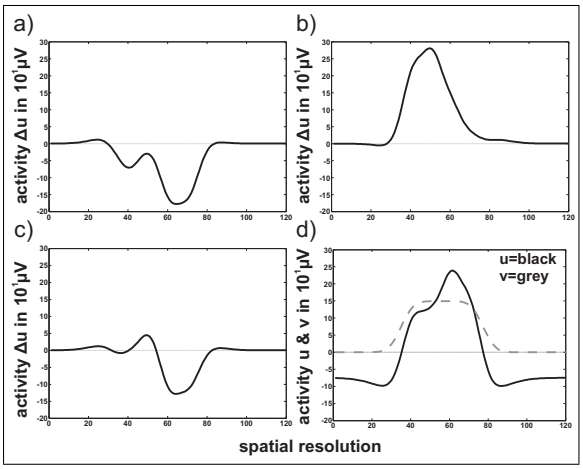

Fig. 2. a-c) Difference in the resulting neural field potential Δu in $(10^1 \mu V)$ after NPs presence in the modeled thalamic neurons for 3 example points in time. d) Representative activity of excitatory field u (black graph) and inhibitory field v (gray dashed line) in $(10^1 \mu V)$ for an example point in time without NPs exposure.

the whole difference field as a function of the simulation time. Compendious, we were able to expand the model introduced

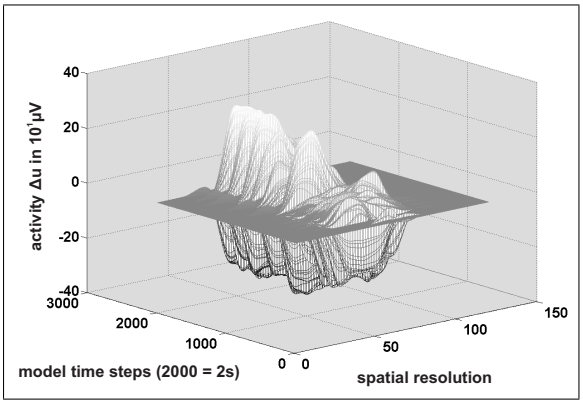

Fig. 3. Resulting neural field difference (Δu) in in $(10^1 \mu V)$ as a function of simulation time.

by Llinás et al. to additionally observe related field potentials that spread over a spatial cortical patch. Incorporating the idea of NPs acting as neuromodulators to this new model, the emerging field potentials of our basic one-dimensional two-layer approach is found to be extensive diversified after presuming the application of NPs to thalamic neurons. In a single neuron model study [1], we could identify the impact of Ag-NPs on the cell's ionic currents. This little change was adopted to model the potential effects of those particles on small sized neuronal feedback circuits in [2]. Even though the observed NPs induced diversifications in the feedback network's signalling behavior was quite small, when integrating the thalamocortical model from a functional column into the dynamics of spatiotemporal neural field potentials, we could observe entirely altered field potentials after particle distribution on few thalamic cells. NPs in thalamic tissue may cause distortions in cortical field potentials, where especially the NSTC cause a spread of these modulatory effects over multiple cortical areas in consequence. This model may subserve as basic approach to estimate the spatiotemporal dynamics of cortical field potentials that may be electrophysiological measurable. In future two-dimensional multi-electrode array - as well as voltage sensitive dye measurements with high spatiotemporal resolution will be carried out by our group on rat auditory cortex. The experimental data will then be applied to compare and also to extend our model with the focus on recovering estimates of the underlying neuronal mechanisms by means of neurons exposed to NPs.

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