Med Biol Eng Comput (2011) 49:511–520
DOI 10.1007/s11517-011-0769-4

SPECIAL ISSUE - ORIGINAL ARTICLE

Spatiotemporal scales and links between electrical neuroimaging modalities

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Received: 15 November 2010 / Accepted: 22 February 2011 / Published online: 12 April 2011

Abstract Recordings of brain electrophysiological activity provide the most direct reflect of neural function. Information contained in these signals varies as a function of the spatial scale at which recordings are done: from single cell recording to large scale macroscopic fields, e.g., scalp EEG. Microscopic and macroscopic measurements and models in Neuroscience are often in conflict. Solving this conflict might require the developments of a sort of bio-statistical physics, a framework for relating the microscopic properties of individual cells to the macroscopic or bulk properties of neural circuits. Such a framework can only emerge in Neuroscience from the systematic analysis and modeling of the diverse recording scales from simultaneous measurements. In this article we briefly review the different measurement scales and models in modern neuroscience to try to identify the sources of conflict that might ultimately help to create a unified theory of brain electromagnetic fields. We argue that seen the different recording scales, from the single cell to the large scale fields measured by the scalp electroencephalogram, as derived from a unique physical magnitude—the electric potential that is measured in all cases—might help to conciliate microscopic and macroscopic models of neural function as well as the animal and human neuroscience literature.

Keywords Local field potential · Mutiunit activity · Single unit activity · Electroencephalography · Electrophysiology · Electrocorticography · Intracranial EEG

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1 Introduction

When Hans Berger reported in 1929 the first measurements of the brain electrical activity in humans: the electroencephalogram (EEG), he described "a continuous wave with continuous oscillations…" that he termed the alpha wave. Faster lower amplitude but also rhythmic activity (beta waves) substituted alpha waves when subjects opened their eyes. However, observing dynamic brain phenomena is one thing and understanding its meaning and functional role quite another. Indeed, while oscillations are currently among the most studied aspects of neural activity, still three major questions continue unanswered today: (1) How are EEG patterns generated? (2) Why are EEG patterns often oscillatory but not always? (3) What are oscillatory patterns useful for?

There is no elementary answer to these questions. Oscillations likely reflect an emergent property of such a complex system as the human brain [16]. Yet, the behavior of a complex system as a whole cannot be easily predicted or deduced from the behavior of individual lower level entities such as neurons. Neither is the outcome simply caused by the summation of its parts, nor is it easy to infer the behavior of the parts from macroscopic observations of the system [15]. Spatiotemporal structure can arise from the interactions of the numerous constituents and

reductionism, i.e., studying neurons in their isolated state must be replaced by an integrated view in modern neuroscience. A fundamental problem of current neuroscience is then to understand the brain through its organization into multiple spatial and temporal scales.

The fact that most neurophysiologists considered neurons as isolated units capable of yielding most of information needed to code/decode features of external stimuli has considerably hindered our understanding of the relationship between electrophysiological signals recorded at different spatial and temporal scales. While technological advances in measuring devices, the interest in neuroprosthetics and brain computer interfaces or the existence of hippocampal place cells have recently stimulated the interest of researchers in understanding what is coded at the diverse scales there is still a huge gap to bridge. Microscopic and macroscopic measurements and models in Neuroscience are often in conflict which is reminiscent of the state of the Physics at the end of the nineteenth century. The conflict was solved with the developments of the statistical physics, a framework for relating the microscopic properties of individual atoms and molecules to the macroscopic or bulk properties of materials. Such a framework can only emerge in Neuroscience from the systematic analysis and modeling of the diverse recording scales from simultaneous measurements. A first step, to which this minireview is addressed, is to understand what are the different electrophysiological signals we have at our disposal, how are they obtained, what is our current interpretation about the role of these signals and their biophysical origins and which interrelationships between scales have been already described.

2 From near to far field electrophysiological measures of neural activity

Nearly in parallel with Berger's discovery of the EEG, Lord Adrian developed techniques for extracellular measurements of single-neurons with microelectrodes [1]. Since then, recording technologies for applied and basic neuroscience applications have significantly improved. Nowadays, we can record electrical activity at different levels ranging from the intracellular space to the scalp surface, using arrays of hundreds of electrodes and amplifiers [10, 73] that cover a wide range of frequencies from "resting" or standing (DC) up to several (50) kHz.

A common factor linking most electrophysiological recordings is the physical magnitude that is measured: the voltage or electrical potential, i.e., the electric potential energy per unit charge, typically expressed in joules per coulomb or simply volts. Note that since the zero of potential can be chosen at any point, the difference in voltage is the quantity which is physically meaningful, i.e., potential is always measured with respect to some reference.

Electrophysiological measurements are commonly subdivided into two categories, near field (intracellular or extracellular) measurements and far field measurements. These terms derive from electrodynamics, where near field and far field are used to denote the different behaviors of the electromagnetic radiation that emanate from an antenna. Note, however, that electromagnetic radiation is not expected to arise at the ultra-low range of frequencies of the electromagnetic fields generated by the brain.

2.1 Near field measurements

2.1.1 Intracellular recordings

Mainly destined to measure voltage (or currents) across the membrane of a cell, the tip (<1 μm) of a sharp microelectrode is used to puncture the membrane without destroying the cell. Voltage is measured with respect to a reference electrode placed within the electrically conducting extracellular fluid that surrounds the cell.

Intracellular potentials are the most sensitive measure to action potentials (APs), i.e., short-lasting (typically less than one ms), uniform pulses (all-or-nothing) of electrical activity used for communication with other neurons and for transmitting information to other body tissues such as muscles and glands. APs are generated when the membrane potential of a neuron reaches a threshold value. They travel down the axon toward synapses terminating at postsynaptic neurons, where they initiate postsynaptic currents (PSCs) that summate to trigger (or inhibit) new APs [40].

2.1.2 Extracellular recordings

Typical near-field extracellular measurements are performed by amplifying the potential difference between the microelectrode tip, placed at the extracellular space, and a reference electrode located within a few millimeters. These recordings are usually broken into two components by filtering (Fig. 1): The local field potential (LFP) corresponds to coherent and relatively slow frequency changes in membrane potential (typically <300 Hz but ranges vary from lab to lab) associated with synaptic currents as well as other sources in cell aggregates, while the higher frequency signal (300–10,000 Hz) consists mostly of multi-unit activity (MUA) resulting from APs in several nearby neurons. By considering the morphology of APs contained in the MUA signal it is possible to isolate the contribution of APs arising from each individual neuron to obtain the single unit activity (SUA). Note that the distinction between LFPs and MUA/SUA is somehow arbitrary as it depends on the frequency cut-offs (e.g., 300 or 500 Hz)

used by each laboratory. While there is a consensus that SUA/MUA activity is spatially localized, over up to 100 μm for the single-unit signals or several hundreds of microns for the multi-unit signals, there are divergent results concerning the spatial extent of LFPs. While some authors consider that the LFP signals can extend over a few millimeters [26] some more recent studies attribute most (95%) of the LFPs signals to local effects generated within the range of some hundreds of microns [49].

LFPs are thought to represent the summed extracellularly recorded voltage fluctuations in the membrane potentials of neuronal population and associated glia cells. LFPs originate from excitatory and inhibitory postsynaptic potentials (EPSP/IPSP), mainly as a result of AP input and therefore provide information about the spatiotemporal activity of afferent, associational, and local operations in a particular brain structure [2].

2.2 Far field measurements

Due to the conducting properties of the extracellular space (volume conduction properties), field potentials propagate throughout the extracellular media and neural tissue and can be measured at the scalp surface or with large electrodes inserted at the extracellular space. This gives rise to the so-called far field measurements encompassing both, invasive and non invasive recordings of neural function:

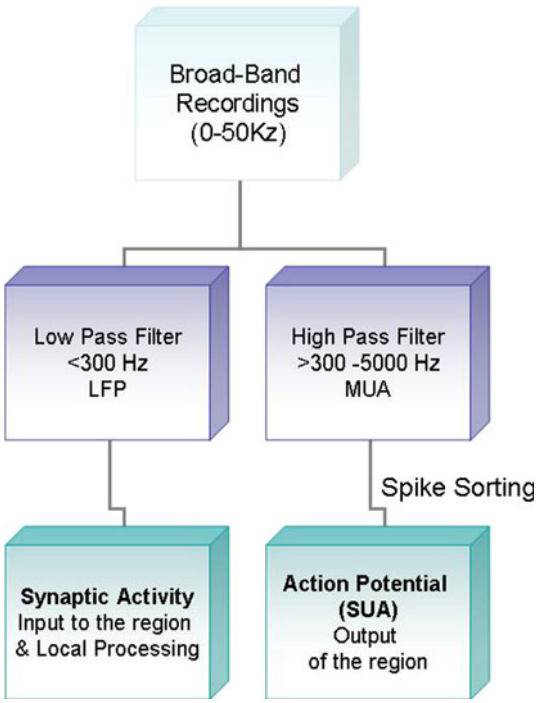

Fig. 1 Near field recordings. Near field potential measurements are currently done using broad band recordings from which field potentials and spiking activity can be obtained by filtering

the intracranial EEG, the electrocorticogram (ECoG), or the scalp (EEG). Additionally, magnetic field recordings can also be measured on the scalp using magnetoencephalography (MEG). For the sake of brevity we exclusively focus here on electrophysiological measurements.

2.2.1 *Deep electrodes EEG (depth-EEG)*

The depth-EEG [55] is recorded by electrodes implanted directly inside the brain of patients typically suffering from: (1) medically intractable epilepsy and (2) Parkinson disease. Typically oriented to detect the anatomical origin of seizures onset or the structure to be lesioned/chronically stimulated, the spatial resolution of depth-EEG depends on the impedance and size of the electrical contacts along the electrodes and also on the volume conduction properties in the piece of brain tissue around the electrode and the placement of the reference [55]. Some recent estimates reviewed in [55] support the view that depth-EEG measures the LFP generated within a centimeter radius.

2.2.2 *ECoG*

During the recording of the ECoG, epi, or subdural arrays of electrodes are used to record field potentials from the cerebral cortex.

Despite cumulated evidence about a functional role and neural origin of high frequency oscillations on scalp EEG (see below), it is typically assumed that far field measurements basically contain significant low-frequency components. Depending on the location and size of the recording and reference electrodes, far field measurements will integrate neural activity over a range of spatial scales that defines its spatial resolution, thought to be better for the deep electrodes EEG, intermediate for the ECoG and worst for the EEG.

2.2.3 *EEG*

The EEG is certainly the oldest neuroimaging technique and is likely to be the most direct correlate of neural activity that can be obtained non-invasively together with the magnetoencephalogram (MEG). The MEG will not be further discussed here as the focus is on electrophysiological signals and the interested reader is referred to [38]. The EEG can be seen as a rough spatial average of microscopic field potentials (LFPs) that are further attenuated by the skull and scalp. Due to the attenuation by the skull and scalp and spatial filtering by volume-conduction in the brain, the spatial resolution of these recordings is presumed to be considerably poorer than near-field recordings.

Compared to the size of the tip of electrodes used for LFP recordings nowadays (a few micrometers in diameter),

the size of sensors used for most clinically oriented invasive recordings in humans is fairly large (2–4 mm in diameter). It becomes therefore difficult to find a relationship between the LFPs and the spiking activity of populations as larger electrodes lump together electric fields from increasingly larger number of neurons. This is why the ECoG and the scalp EEG reflect spatially smoothed versions of the LFPs at numerous contiguous sites and have relatively poor relationship with spiking activity of individual neurons [15, 26].

Examples of simultaneously recorded electrophysiological signals in rats illustrating the different spatial scales are given in Fig. 2. The picture shows 1.5 s of EEG recordings (lower most) from an electrode placed directly above the barrel cortex at the exposed dura (Dura-EEG). On top, we show the three signals that are typically extracted through standard filtering operations from the voltage recorded by an extracellular electrode inserted within the rat somatosensory (barrel) cortex (C-MUA, C-EEG(500–2000) Hz, CEEG (0–300) Hz). These operations give rise to three signals, namely, (1) The slow frequency part of the voltage corresponding to the LFP signal obtained after bandpass filtering within the 0–300 Hz range, (2) The high frequency part (500–2000 Hz) of the extracellular potentials that contains most of the APs generated in the neighborhood of the electrode tip, and (3) a binary signal (MUA) that indicates the time of onset of APs detected at the extracellular space after thresholding the high frequency part of the recorded voltage.

The perils of restricting the analysis and interpretation of neural data to a single recording scale are clearly illustrated in Fig. 2. The continuous EEG traces show a rich temporal variation that is missed by any analysis that exclusively considers the timing and frequency of APs. For instance, there is no apparent reflect on the cortical data of the activity seen in dura during the periods marked by the thick black arrows. On the other hand, the C-EEG (0–300) Hz and the dura EEG are dominated by the low frequency components—due to their large amplitude—which obscure the contribution of multiple or single cells. Coding mechanisms in the CNS, discussed next, might combine features contained in signals at different recording levels. Focusing exclusively on single or multiple cell activity as the elements of the code automatically implies assuming that the well organized oscillations commonly seen in the EEG recordings in animals and humans are noise.

2.3 What information is coded at each level of recording?

Understanding the neural code, i.e., how do single cells or populations determine the stimuli and lead to timely response constitutes an extensively debated and fascinating problem that will prove fundamental in trying to understand how the brain processes information [4, 48]. At the near field level, there is considerable experimental evidence supporting the idea that sequences or trains of APs represent somehow the features of the stimuli in sensory cortices or specify the kinematics or dynamics of motor actions. Nevertheless, the nature of this representation is still unclear in most sensory systems as trains of APs show considerable trial to trial variability in the presence of identical stimuli or responses. Coding mechanisms seem even more complex within association cortices or subcortical structures that might apparently represent more abstract concepts such as for instance the anticipated reward [68].

The idea that the primary function of a neural population is to convey information about the stimulus have been questioned by authors who argue that cortical circuits show complex dynamics even in the absence of sensory stimulation [3, 15, 26, 50]. Indeed, part of the variability across trials observed in neural responses might have its origin in the state of the network before the stimulus is presented. Favoring this interpretation, there is experimental evidence showing that ongoing activity that precedes sensory stimulation plays an important part in shaping neural activity during stimulus presentation [26, 31]. Consequently, it might be more accurate and fruitful to understand the neural code to regard sensory stimuli as modulating the ongoing neural dynamics, rather than deterministically leading to established response patterns of APs that encode all physical features of the stimuli [15].

Understanding what is coded in field potentials recorded in the near or far field has proven even more difficult than understanding the code in single cells or populations. The fact that the exact relationship between the LFP and MUA is still far from clear [14, 54, 58] do complicate things. One of the most widespread models presupposes that LFP mainly reflects postsynaptic potentials and therefore represents the input to a neuronal network and MUA the spiking output [58]. According to this hypothesis, the LFP supplies the external drive and the MUA is a response to that drive through the filtering of the thresholds of the cells and spike-firing mechanisms [13, 14, 57]. This hypothesis has been recently questioned [13] as the coherence between LFP and MUA remains weak on fine temporal scales suggesting that the relation between MUA and the LFP may be more complex than simply the input to and output from the locally recorded network. Nevertheless, most of the studies hitherto done rely on finding dependencies between MUA and LFP recorded within the same electrode. However, experimentally testing if the aforementioned input (LFP)/output (MUA) interpretation is correct is likely to require recordings on two different areas that are synaptically connected. In fact, we should expect that if

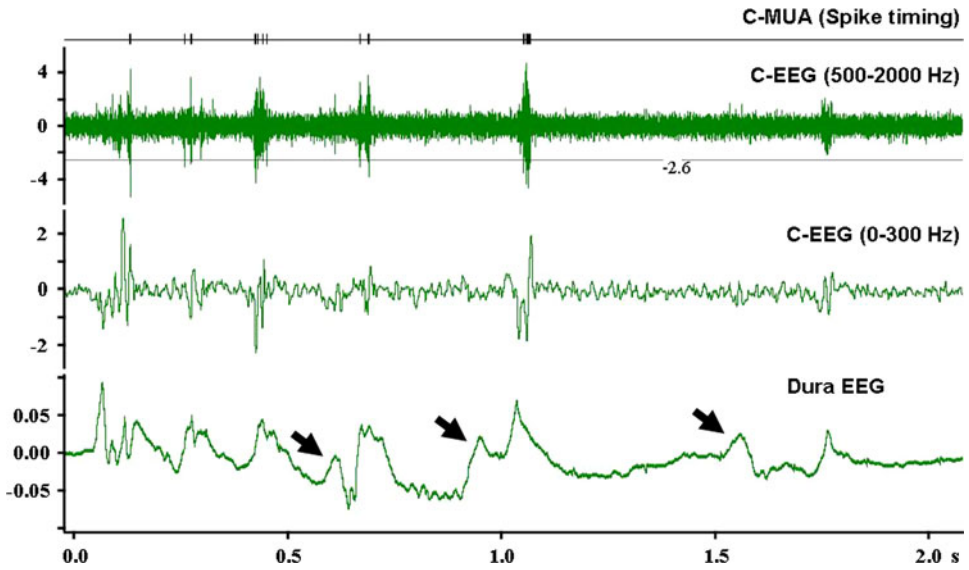

Fig. 2 Simultaneously recorded electrophysiological signals at different spatial scales. (Data courtesy of Prof. F. Panetsos). The low trace (Dura EEG) is the EEG recorded from an electrode placed at the exposed dura (D) directly over the rat barrel cortex. On top of it we show the signals derived from extracellular recordings at one electrode within the barrel cortex (C-MUA and C-EEG) trough the standard filtering operations described in Fig. 1. C-EEG (500–2000)Hz and C-EEG (0–300) Hz *traces* represent the extracellular data filtered within the LFP band and MUA band using a bandpass filter. The *uppermost trace* indicates the MUA obtained after thresholding the extracellular signal filtered in the high frequency range. Note that there are long periods where no action potentials are recorded by the extracellular electrode but still consistent fluctuations on the EEG activity at dura are seen (indicated by *arrows*)

the hypothesis is true, the MUA (output) from the area that supplies the external drive and sent afferent information, correlates with at least part of the LFPs (input) in the area receiving the information. To our knowledge, this analysis is still missing.

In line with the reductionism that permeated neuroscience until the 1980s, many researchers are still skeptical about whether neural oscillations, even if a hallmark of cortical network dynamics [16], play a functional role or are a mere byproduct of other more important neural mechanism. The main argument against synchrony, i.e., the simultaneous firing of several neurons, is that it occurs over short time windows as to reliably encode anything. Irrespective of the functional role that oscillations and synchrony might play it is interesting to learn that the default pattern of single neurons isolated from network connections is oscillatory. Indeed, pharmacologically blocking the receptors responsible for excitation and inhibition in the hippocampus [15, 19], lead to much higher rates and more rhythmic firing in individual neurons. In humans, the largest amplitude and most regular spontaneous oscillations in the cerebral cortex occur during sleep, anesthesia, in newborns, or when the brain is disengaged from the environment and body, i.e., when cognitive operations and sensory input/output are reduced to a minimum (e.g., strong alpha oscillations are recorded at the occipital cortex upon closing the eyes, see Fig. 3) and are modulated by cognitive operations and even unperceived sensory stimuli.

In summary, rhythmic patterns of discharges spontaneously emerge in isolated cells and populations and can be measured in near and far field recordings. However, it is not yet completely clear why engaging into certain networks computations tends to abolish this spatiotemporal structure. The book "Rhythms of the brain" [15] constitutes an excellent review on the roles proposed to be accomplished by network oscillations, namely, (1) bias input selection, (2) temporally link neurons into assemblies, and (3) facilitate synaptic plasticity. Another excellent review in this issue can be found in Engel [26].

In what concerns the study of the functional role of oscillatory activity detected in far field recordings in humans, research has mainly focused on relatively slow oscillatory activity within conventionally predefined frequency bands: theta 4–8 Hz, alpha 8–12 Hz, beta 13–25 Hz, and gamma 26–80 Hz. For the sake of brevity we will not further discuss here main findings concerning slow oscillations and refer the interested readers to: [52, 61, 74]. We prefer to briefly focus on the so called epsilon neural oscillations [27] above 100 Hz, as the topic has been much less investigated and fast oscillations are more likely to encode information about physical features of the stimuli on highly dynamic processes.

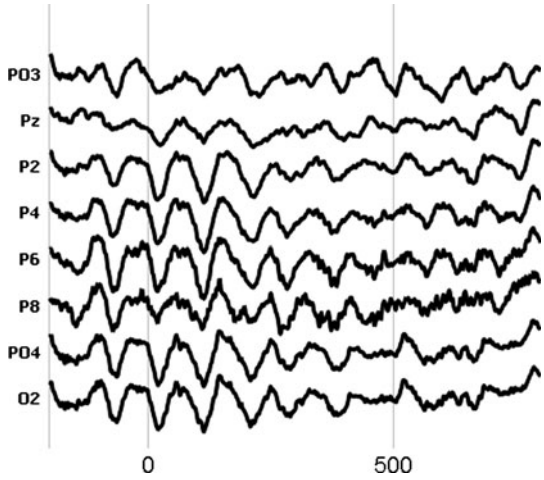

Fig. 3 Ongoing EEG oscillations in the alpha band are modified by non-consciously perceived stimuli. The figure shows single trial EEG traces recorded at the occipital cortex while a subject waits (in the whole darkness) for the onset of a visual stimuli. The stimulus (presented at 0) consists on a controlled pulse of photons of 1 ms duration. The data shown correspond to a trial where the subject failed to perceive the flash. Note that the ongoing alpha oscillations are modified by the onset of the flash even if there is no conscious perception

The observation of neural epsilon oscillations is a relatively new finding. Initially observed in rat's hippocampus during sleep [17], they were coined ripples and are supposed to elicit the information transfer between the hippocampus and neocortex [69]. In rats [5] high frequency oscillations in the somato-sensory cortex of around 200 Hz are supposed to extract features of an object under exploration. In humans, evidence for very high frequency oscillations comes from intracranial recordings in epileptic patients [11, 25] and scalp EEG/MEG [20, 21, 34]. Interestingly, in a recent intracranial study, only the high gamma and epsilon band activities (60–200 Hz) were able to distinguish the two different roles of the premotor cortex, that is, to separate motor intention from attention/memory. Also in humans, Canolty and co-workers [18] showed coupling between the power of high frequency epsilon oscillations around 150 Hz and theta oscillation power and phase. The observed coupling varied with the behavioral task leading the authors to conclude "that cross-frequency coupling between distinct brain rhythms facilitates the transient coordination of cortical areas required for adaptive behavior in humans". Simultaneous MUA and LFPs in monkeys' inferior-temporal cortex revealed that LFP oscillations in the range 100-300 Hz are the ones that best correlate with MUA [53]. Finally, several observations suggest that spontaneous very high frequency oscillations are not present in developing networks [56]. In rat pups, physiological ripple oscillations >140 Hz are observed in vivo in the hippocampus only after the end of the second postnatal week [12].

The relationship between the low frequency part (0–300 Hz) of the LFPs and MUA remains much less studied and understood. It is, however, clear that that neurons, apart from generating fields, are also sensitive to them [45, 75]. In other words, cells are sensitive to changes in the extracellular fields and therefore the weak electric fields that are generated endogenously by physiological network activity have a significant effect on the constituent neurons [28, 59]. Intracellular recordings have shown that on isolated cultures [67] or during for example anesthesia or slow-wave sleep [36, 41] membrane potentials switch between de- and hyperpolarized levels—the cortical UP and DOWN states—and SUA or MUA elicited by sensory stimuli fluctuates with these states [28]. Consequently, network activity likely to be reflected in the slow frequency part of LFPs modulates high frequency activity (SUA/MUA). For instance, UP/DOWN states in deep cortical layers of rat primary auditory cortex (A1) are predictable from the phase of LFP at low frequencies (<4 Hz) and the likelihood of a given state varies sinusoidally with the phase of LFP at these frequencies [66].

Our understanding on the information encoded in field potentials has been stimulated by research in the neuroprosthetic field. In neuroprosthetics, the main goal is to decode the intentions of a subject on the only basis of his/her neural signals as to allow for the precise control of interfaces bypassing the traditional communication pathways via muscles. Since information needs to be decoded in real time and therefore on single trials there have been an urge—on non-invasive human neuroscience—to abandon the most traditional averages over many repetitions (event related potentials or ERPs) replacing them by multivariate pattern recognition (MPR) approaches. In parallel, invasive neuroprosthetics has started to investigate how to better exploit the information contained in LFPs for device control as these signals are easy to record, and more stable, with invasive multielectrode arrays (MEA) than MUA/SUA. Studies in animals using intracerebral invasive recordings of LFP show that reproducible information about neural processes is coded within the temporal structure of LFPs in the form of oscillatory activity. This information has been shown to be as efficient as the information carried by the spike rate of individual neurons in predicting animal behavior [60, 64] or cognitive states [29, 64]. Non invasive studies in humans that rely on a combination of MPR and the non-invasive estimation of depth-EEG/LFP from scalp recorded data [22, 30, 31, 35] have shown that perceptual [32] or behavioral [34] states of the subjects can be accurately decoded on a single trial basis from the OA estimated within the brain on the basis of short (200–500 ms) analysis windows. Moreover, a similar procedure allowed to shed light on the implicit perceptual capabilities and pathways involved in

discriminating facial expressions in blindsight patient able to identify (above chance) the affective content of faces without awareness [33].

3 Modeling across scales

Literature in neuroscience that tries to frame into models the relationships between the microscopic (most near field) and macroscopic (far field) scales is relatively scarce. Models describing the generation of macroscopic fields as measured by the EEG, the intracerebral field potentials (LFPs), and the MEG can be encompassed into two broad classes: (1) neural mass models or network models [23, 43, 46, 47] that aim to describe the complex connectivity of neural networks and their excitatory and inhibitory interconnections and (2) electromagnetic models (EM models) that rely on the macroscopic version of Maxwell equations and are typically used for source imaging and modeling of field propagation in neural tissue. Neural mass models emphasize the local effects of the neural circuitry on the network dynamic but often disregard the long distance effects of macroscopic fields. As seen next, most EM models are physically inconsistent since electromagnetic wave (EMW) propagation is completely incompatible with the quasi-static approximation they rely on.

Contrarily to microscopic models of the membrane potential based on Hodking-Huxley equations which have traveling waves as solutions [39] or the neural mass models, the EM models for EEG/MEG/LFPs preclude it. The cornerstone of current EM models is indeed the quasi-static approximation (QSA) [65] of Maxwell equations where a snapshot of the source distribution determines the field distribution at the same instant without regard for what the sources of fields were an instant earlier. A direct consequence of working under the quasi-static regime is that there is no EMW propagation [44], leading to a conflict between the microscopic and macroscopic formulations. This contradiction between the models ruling electromagnetic phenomena at different spatial scales is deeply disturbing.

The QSA is an approximation of the physical reality aimed to simplify Maxwell equations and which has been omnipresent in the modeling of macroscopic EEG (and MEG) phenomena since its original formulation [65]. As an approximation, it is of limited validity and should be probably abandoned since incompatible with both, experimental evidence and microscopic models.

There is a second simplification in current EM models at all recording scales, i.e., from LFPs to EEGs, that consist in assuming that sources of the fields are embedded in piecewise homogeneous and isotropic media. Under this approximation extracellular potentials should not exhibit any frequency-dependent attenuation with distance [7]. However, as argued before, experimental results suggest that the spatial extent of SUA/MUA is smaller than that of the slower LFPs which is in contradiction with this model. On the other hand, modeling results show that the extracellular potential can display frequency-dependent attenuation, but only if the extracellular conductivity is non-homogeneous [7], and as a consequence there is induction of non-homogeneous charge densities which may result in a low-pass filter. Therefore, the assumption of a piecewise homogeneous medium is probably too simplistic to correctly reproduce the experimentally observed frequency-dependency properties of LFPs and in particular the induced electric fields in the non-homogeneous extracellular tissue [8] and requires further consideration.

A promissory model has been recently developed [6] which still relies on Maxwell equations but which naturally incorporate macroscopic measurements of permittivity and conductivity. This study stressed the importance of ionic diffusion to reproduce the decrease in power with increasing frequency ("$1/f$") dependence of electric parameters observed experimentally. Accounting for ionic diffusion, even if still limited to the near field measured LFPs, is already a way to partially restore the compatibility between microscopic and macroscopic models as temporal dependencies—in the form of derivatives with respect to time—cannot be anymore ignored.

4 Wave phenomena in neural tissue

Synaptic transmission (ST) remains the most widespread and better studied mechanism of neural communication. ST operates over short spatial scales transmitting information between neighboring cells. Despite substantial progress in understanding the CNS achieved in the last decades, we are still missing some pieces of the puzzle. Spatially segregated brain areas simultaneously process diverse aspects of sensory stimuli. How is this scattered information coordinated and bound together to give rise to coherent percepts and actions?

Neural synchrony in cortical networks has been proposed as a general mechanism for the coordination of distributed neural activity patterns. While there is little doubt that oscillations and synchrony are ubiquitous phenomena in the CNS, the issue of long range communication and particularly that of zero lag synchrony is not yet solved by this proposal. Long distance synchrony among spatially segregated areas cannot be driven by local oscillations alone. We need a mechanism that explains the nearly instantaneous transport of information across the space so that cells in distant and often unconnected areas become synchronized. EMW propagation in neural tissue could solve this issue.

Electromagnetic waves and neural oscillations (e.g., in the theta, alpha, or gamma range) are not the same even if the terms are often intermingled in the literature. Oscillations measured in field potential recordings tell us that the local sources of the field are varying in time. The neural mechanisms behind the temporal variations can be very diverse and reflect a purely local phenomenon, the coordinated action of an interconnected brain network or the effects of an EMW that travels in the medium.

Oscillations per se do not transmit information in space or necessarily reflect any action at a distance. In contrast, an EMW affects its surroundings as it travels throughout it carrying energy and momentum. When a wave travels through a medium (as for example neural tissue), the bounded particles (molecules bounded to the cell membrane) cannot move along with it as free molecules do [71]. The EMW polarizes the bounded molecules creating a net dipolar moment and a displacement current. Displacement currents are essential to EMW propagation. Bounded molecules vibrate about their equilibrium position, and the energy is transmitted over long distances through the interaction of neighboring particles. The vibration of the particles around equilibrium is perceived as an oscillation. Evidence for the existence of bounded molecules and the creation of dipolar moments in the CNS is relatively old. For example, it has been shown that a large fraction of the total capacitance measured in the squid giant axon membrane arises from reorientation of charged or dipolar groups residing in the membrane itself [72]. Variations in these dipolar groups from cell to cell might explain that synchronization becomes selective and does not involve cells in the whole brain. Different dipolar groups might have different resonance frequency preferences as a function of the physical properties of the membrane-bound charged molecule and therefore selectively sustain oscillations only when driven by inputs near their resonant frequency [42]. Wave propagation in neural tissue can therefore open the door to selective non-synaptic information transmission [24, 45], i.e., to the exchange of information between distant areas that are not necessarily hard-wired [63]. Because neural tissue is highly inhomogeneous, wave scattering is very likely to occur. Mechanisms like resonance or oscillation can therefore operate over a vast range of time scales and a vast range of distances.

Developments in neuroimaging modalities such as optical imaging are leading to an accumulating body of evidences supporting the existence of EMW propagation phenomena in the brain [23, 46, 62]. However, the existence of EMW was postulated long time ago by researchers studying the dynamic of the EEG [62].

Probably, the earliest experimental evidences for EMW propagation in the brain can be traced back to 1944 in the so-called cortical spreading depression (SD) [70]. At the core of SD is a rapid and nearly complete depolarization of a sizable population of brain cells with massive redistribution of ions between intracellular and extracellular compartments, which evolves as a regenerative, "all-or-none" type process and propagates in the manner of a wave through gray matter. A similar response occurs in cerebral gray matter a few minutes after interruption of the blood flow or of the supply of oxygen.

In the last 4 years, ample evidence for a link between EMW waves in visual areas and visual processing has been uncovered. EM brain waves are seen already at the level of the retina [51]. Standing, traveling, or reflected EMW have been observed in the visual cortex of cats [9] and rats [37, 76] in response to visual stimuli and seemingly represent functional neurocircuitry.

5 Discussion

In this paper we briefly review diverse electrophysiological measures of neural activity in an attempt to integrate them across spatial recording scales. Some of the main experimental findings concerning the information encoded at each scale are described to support the idea that large scale fields are not a byproduct of single cell activity but rather reflect the structure imposed by the large scale organization of the brain into functional networks and the dynamic interaction of these networks with the neural tissue.

We sustain here the view that the lack of models of the brain electromagnetic activity able to fuse spatial scales hinders a unified picture of electrophysiology across scales and species. A first step is to understand that a unique physical quantity—the electric potential—is measured and that Maxwell equations in its full extent provide the adequate conceptual framework to start developing models. However, a unified picture cannot emerge if the main assumptions behind microscopic and macroscopic models are in contradiction. We here uncover one contradiction between quasi-static macroscopic models of EEG/MEG/LFPs on the one hand and the microscopic models and the experimental evidence for wave propagation on the other. We believe that the solution to this contradiction passes by developing a physically sound model describing how microscopic ionic currents (as in the Hodking-Huxley formulation) interact with the neural tissue to lead to macroscopic fields. This proposal restores the compatibility of the microscopic and macroscopic formulations of electromagnetic brain phenomena on the one hand and the experimental evidences for EMW propagation in neural tissue on the other.

It is likely that the development of unified models helps to solve one of the long standing question for the Neurosciences. Unified models could help to determine if (and if

ever how) the brain exploits the diverse wave propagation phenomena (e.g., traveling, standing, or reflected waves) for non-synaptic information transmission. Waves might provide a natural explanation for experimental findings in neuroscience such as the persistently observed inverse relationship between the spatial extent of field potential oscillations and their frequencies. According to the dispersion relations, in waves, higher spatial frequencies must accompany higher temporal frequencies. Importantly, progresses in developing models passes by obtaining a much better characterization of the electrical parameters of neural tissue and their variations with frequency as they are the basis of the constitutive relationships in Maxwell equations that relate macroscopic to microscopic fields.

Acknowledgments We thank Prof. Fivos Panetsos, Laboratory of Neurocomputing and Neurorobotics, Complutense University of Madrid, Spain for graciously providing the data shown in Fig. 2. This study has been supported by the 3R Research Foundation, Switzerland, under Grant number 119-10. We thank two anonymous reviewers for their detailed comments that contributed to improve earlier versions of this manuscript.

References

1. Adrian ED, Matthews BHC (1934) The interpretation of potential waves in the cortex. J Physiol 81:440–471
2. Anastassiou CA, Montgomery SM, Barahona M, Buzsaki G, Koch C (2010) The effect of spatially inhomogeneous extracellular electric fields on neurons. J Neurosci 30:1925–1936. doi:10.1523/JNEUROSCI.3635-09.2010
3. Arieli A, Sterkin A, Grinvald A, Aertsen A (1996) Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273:1868–1871
4. Averbeck BB, Lee D (2004) Coding and transmission of information by neural ensembles. Trends Neurosci 27:225–230
5. Barth DS (2003) Submillisecond synchronization of fast electrical oscillations in neocortex. J Neurosci 23:2502–2510
6. Bedard C, Destexhe A (2009) Macroscopic models of local field potentials the apparent 1/f noise in brain activity. Biophys J 96:2589–2603
7. Bedard C, Kroger H, Destexhe A (2004) Modeling extracellular field potentials and the frequency-filtering properties of extracellular space. Biophys J 86:1829–1842
8. Bedard C, Kröger H, Destexhe A (2006) Model of low-pass filtering of local field potentials in brain tissue. Phys Rev E 73:051911
9. Benucci A, Frazor RA, Carandini M (2007) Standing waves and traveling waves distinguish two circuits in visual cortex. 55:103–117
10. Blum RA, Ross JD, Brown EA, DeWeerth SP (2007) An integrated system for simultaneous, multichannel neuronal stimulation and recording. IEEE Trans Circuits Syst 54:2608–2618
11. Brovelli A, Lachaux LJ, Kahane P, Boussaoud D (2005) High gamma frequency oscillatory activity dissociates attention from intention in the human premotor cortex. Neuroimage 28:154–164
12. Buhl DL, Buzsaki G (2005) Developmental emergence of hippocampal fast-field "ripple" oscillations in the behaving rat pups. Neuroscience 134:1423–1430
13. Burns SP, Xing D, Shapley RM (2010) Comparisons of the dynamics of local field potential and multiunit activity signals in macaque visual cortex. J Neurosci 30:13739–13749. doi:10.1523/JNEUROSCI.0743-10.2010
14. Buzsáki G (2002) Theta oscillations in the hippocampus. Neuron 33:325–340
15. Buzsáki G (2006) Rhythms of the brain. University Press, Oxford
16. Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926–1929
17. Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K (1992) High-frequency network oscillation in the hippocampus. Science 256:1025–1027. doi:10.1126/science.1589772
18. Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT (2006) High gamma power is phase-locked to theta oscillations in human neocortex. Science 313:1626–1628. doi:10.1126/science.1128115
19. Cohen I, Miles R (2000) Contributions of intrinsic and synaptic activities to the generation of neuronal discharges in in vitro hippocampus. J Physiol 524(2):485–502
20. Curio G (2000) Linking 600-Hz "spikelike" EEG/MEG wavelets ("sigma-bursts") to cellular substrates: concepts and caveats. J Clin Neurophysiol 17:377–396
21. Curio G, Mackert BM, Burghoff M, Koetitz R, Abraham-Fuchs K, Harer W (1994) Localization of evoked neuromagnetic 600 Hz activity in the cerebral somatosensory system. Electroencephalogr Clin Neurophysiol 91:483–487
22. Deco G, Jirsa VK, Robinson PA, Breakspear M, Friston K (2008) The dynamic brain: from spiking neurons to neural masses and cortical fields. PLoS Comput Biol 4:e1000092
23. Draguhn A, Traub RD, Schmitz D, Jefferys JG (1998) Electrical coupling underlies high-frequency oscillations in the hippocampus in vitro. Nature 394:189–192
24. Edwards E, Soltani M, Deouell LY, Berger MS, Knight RT (2005) High gamma activity in response to deviant auditory stimuli recorded directly from human cortex. J Neurophysiol 94:4269–4280. doi:10.1152/jn.00324.2005
25. Engel AK, Fries P, Singer W (2001) Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2:704–716
26. Freeman WJ (2007) Definitions of state variables and state space for brain-computer interface—part 1: multiple hierarchical levels of brain function. Cogn Neurodyn 1:3–14
27. Fröhlich F, McCormick DA (2010) Endogenous electric fields may guide neocortical network activity. Neuron 67:129–143
28. Gervasoni D, Lin SC, Ribeiro S, Soares ES, Pantoja J, Nicolelis MA (2004) Global forebrain dynamics predict rat behavioral states and their transitions. J Neurosci 24:11137–11147
29. Gonzalez Andino SL, Grave de Peralta Menendez R, Lantz CM, Blank O, Michel CM, Landis T (2001) Non-stationary distributed source approximation: an alternative to improve localization procedures. Hum Brain Mapp 14:81–95
30. Gonzalez Andino SL, Michel CM, Thut G, Landis T, Grave de Peralta R (2005) Prediction of response speed by anticipatory high-frequency (gamma band) oscillations in the human brain. Hum Brain Mapp 24:50–58
31. Gonzalez Andino SL, Grave de Peralta R, Khateb A, Pegna AJ, Thut G, Landis T (2007) A glimpse into your vision. Hum Brain Mapp 28:614–624
32. Gonzalez Andino SL, Grave de Peralta Menendez R, Khateb A, Landis T, Pegna AJ (2009) Electrophysiological correlates of affective blindsight. NeuroImage 44:581–589
33. Gonzalez SL, Grave de Peralta R, Thut G, Millan Jdel R, Morier P, Landis T (2006) Very high frequency oscillations (VHFO) as a predictor of movement intentions. Neuroimage 32:170–179

34. Grave de Peralta Menendez R, Gonzalez Andino SL (2000) Two new alternatives to compute smooth solutions. NeuroImage 11:S486
35. Grave de Peralta Menendez R, Gonzalez Andino SL, Morand S, Michel CM, Landis T (2000) Imaging the electrical activity of the brain: ELECTRA. Hum Brain Mapp 9:1–12
36. Haider B, Duque A, Hasenstaub AR, McCormick DA (2006) Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. J Neurosci 26:4535–4545
37. Han F, Caporale N, Dan Y (2008) Reverberation of recent visual experience in spontaneous cortical waves. Neuron 60:321–327
38. Hari R, Parkkonen L, Nangini C (2010) The brain in time: insights from neuromagnetic recordings. Ann N Y Acad Sci 1191:89–109
39. Hastings SP (1976) On travelling wave solutions of the Hodgkin-Huxley equations. Arch Ration Mech Anal 60:229–257
40. Hille B (1970) Ionic channels in nerve membranes. Prog Biophys Mol Biol 21:1–32
41. Hoffman KL, Battaglia FP, Harris K, MacLean JN, Marshall L, Mehta MR (2007) The upshot of up states in the neocortex: from slow oscillations to memory formation. J Neurosci 27:11838–11841
42. Hutcheon B, Yarom Y (2000) Resonance, oscillation and the intrinsic frequency preferences of neurons. Trends Neurosci 23:216–222
43. Ingber L (1994) Statistical mechanics of neocortical interactions: path-integral evolution of short-term memory. Phys Rev E 49:4652–4664
44. Jackson JD (1998) Classical electrodynamics. Wiley, New York
45. Jefferys JG (1995) Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. Physiol Rev 75:689–723
46. Jirsa VK, Haken H (1996) Field theory of electromagnetic brain activity. Phys Rev Lett 77:960–963
47. Jirsa V, Jantzen K, Fuchs A, Kelso J (2002) Spatiotemporal forward solution of the EEG and MEG using network modeling. IEEE Trans Med Imag 21:493–504
48. Johnson KO (2000) Neural coding. Neuron 26:563–566
49. Katzner S, Nauhaus I, Benucci A, Bonin V, Ringach DL, Carandini M (2009) Local origin of field potentials in visual cortex. Neuron 61:35–41
50. Kenet T, Bibitchkov D, Tsodyks M, Grinvald A, Arieli A (2003) Spontaneously emerging cortical representations of visual attributes. Nature 425:954–956
51. Kerschensteiner D, Wong ROL (2008) A precisely timed asynchronous pattern of ON and OFF retinal ganglion cell activity during propagation of retinal waves. Neuron 58:851–858
52. Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev 2–3:169–195
53. Kreiman G, Hung C, Quian Quiroga R, Kraskov A, Poggio T, DiCarlo JJ (2006) Object selectivity of local field potentials and spikes in the macaque inferior temporal cortex. Neuron 49:1–13
54. Kruse W, Eckhorn R (1996) Inhibition of sustained gamma oscillations (35–80 Hz) by fast transient responses in cat visual cortex. Proc Natl Acad Sci USA 93:6112–6117
55. Lachaux JP, Rudrauf D, Kahane P (2003) Intracranial EEG and human brain mapping. J Physiol Paris 97:613–628
56. Le Van Quyen M, Khalilov I, Ben-Ari Y (2006) The dark side of high-frequency oscillations in the developing brain. Trends Neurosci 29:419–427
57. Logothetis NK, Wandell BA (2004) Interpreting the BOLD Signal. Annu Rev Physiol 66:735–769
58. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157
59. Mann EO, Paulsen O (2010) Local field potential oscillations as a cortical soliloquy. Neuron 67:3–5
60. Mehring C, Rickert J, Vaadia E, Cardosa de Oliveira S, Aertsen A, Rotter S (2003) Inference of hand movements from local field potentials in monkey motor cortex. Nat Neurosci 6:1253–1254
61. Niedermeyer E, Lopes da Silva F (2004) Electroencephalography: basic principles, clinical applications, and related fields. Lippincott Williams & Wilkins, New York
62. Nunez PL, Srinivasan R (2005) Electric fields of the brain: the neurophysics of EEG. Oxford University Press, New York
63. Nunez PL, Srinivasan R (2006) A theoretical basis for standing and traveling brain waves measured with human EEG with implications for an integrated consciousness. Clin Neurophysiol 117:2424–2435
64. Pesaran B, Pezaris JS, Sahani M, Mitra PP, Andersen RA (2002) Temporal structure in neuronal activity during working memory in macaque parietal cortex. Nat Neurosci 5:805–811
65. Plonsey R, Heppner DB (1967) Considerations of quasistationarity in electrophysiological systems. Bull Math Biophys 29:657–664
66. Saleem AB, Chadderton P, Apergis-Schoute J, Harris KD, Schultz SR (2010) Methods for predicting cortical UP and DOWN states from the phase of deep layer local field potentials. J Comput Neurosci 29:49–62. doi:10.1007/s10827-010-0228-5
67. Sanchez-Vives MV, McCormick DA (2000) Cellular and network mechanisms of rhythmic recurrent activity in neocortex. Nat Neurosci 3:1027–1034
68. Schultz W (2010) Dopamine signals for reward value and risk: basic and recent data. Behav Brain Funct 6:24
69. Sirota A, Csicsvari J, Buhl D, Buzsaki G (2003) Communication between neocortex and hippocampus during sleep in rodents. PNAS 100:2065–2069. doi:10.1073/pnas.0437938100
70. Somjen GG (2001) Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiol Rev 81:1065–1096
71. Syková E, Nicholson C (2008) Diffusion in brain extracellular space. Physiol Rev 88:1277–1340
72. Taylor RE, Fernândez JM, Bezanilla F (1982) Squid axon membrane low frequency dielectric properties. In: Adelman WJ, Goldman DE (eds) The biophysical approach to excitable systems. Proceedings of symposium honoring Kenneth S. Cole on his 80th birthday. Plenum Press, New York, pp 97–106
73. Teplan M (2002) Fundamentals of EEG measurement. Measurement Sci Rev 2:1–11
74. Uhlhaas PJ, Singer W (2010) Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11:100–113
75. Weiss SA, Faber DS (2010) Field effects in the CNS play functional roles. Front Neural Circuits 18:4–15
76. Xu W, Huang X, Takagaki K, Wu J-y (2007) Compression and reflection of visually evoked cortical waves. Neuron 55:119–129