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Physica C 368 (2002) 50–54

PHYSICA C

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High T_c SQUID systems for magnetophysiology

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Abstract

Magnetophysiology is the use of a superconducting quantum interference device (SQUID) based instrument to detect neuromagnetic fields evoked by electrical stimulation of brain tissue slices. In this paper we show that a SQUID based on high temperature superconductors (HTSs) would have considerable advantages over a low T_c device in this application. We construct a model of electrical activity in a hippocampal brain slice, which enables the neuromagnetic field to be determined as a function of position and distance from the tissue. We then describe the design of HTS SQUID systems for magnetophysiology and the two styles of system we are developing. Finally we use our model to show that an existing HTS SQUID magnetometer would give a superior signal to noise ratio compared to a low T_c system for the hippocampal brain slice preparation at least. © 2001 Published by Elsevier Science B.V.

Keywords: Biomagnetism; SQUIDs; Neuromagnetism

1. Introduction

Commercial magnetoencephalography (MEG) systems, involving several hundred SQUID channels, are routinely used to detect the magnitude and spatial distribution of the neuromagnetic field close to the scalp. The magnitude of the signal (typically 0.1 pT) and its distribution, suggest that the coherent activity of as many as 10^5 neurons is involved [1]. As a result, the detailed waveforms produced must depend upon the mutual interconnection (which can be either excitatory or inhibitory) of a number of types of cell. Thus, the complexity of the neuronal networks in the intact brain contribute to the problems of interpreting the in vivo MEG and understanding its cellular origins.

At the single cell level, neuronal activity has been investigated for many years [2]. By inserting an electrode inside a cell in vitro, one cannot only detect the action potential (AP), but directly measure the post synaptic potential (PSP) and post synaptic current (PSC) which initiate the AP. The direction and magnitude of the PSC are fixed by the combined effect of a set of inhibitory or

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0921-4534/02/$ - see front matter © 2001 Published by Elsevier Science B.V.
PII: S0921-4534(01)01139-X

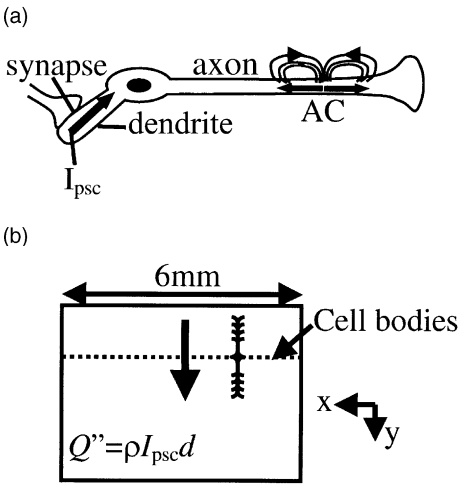

Fig. 1. Diagrams to show the structure of (a) a simplified neuronal model (AC indicates ionic currents associated with an AP) and (b) the hippocampal slice model used to calculate B_z as a function of position.

excitatory stimuli at synapses between neurons, which determine the PSP level and hence whether or not the cell fires. These stimuli are mediated by neurotransmitters and modulated by chemicals in the vicinity of the synapse (see Fig. 1a). Hence the measurement of PSCs in vitro is a key technique of modern neuroscience. However, the use of an intracellular electrode is very invasive and destructive to the recorded neuron. An alternative technique, which was significantly less invasive, would therefore be very attractive.

Recently Okada et al. [3] have employed a low T_c BTi microSQUID system to investigate the origin of the MEG signal in Guineapig hippocampal brain slices. With a minimum source to sensor separation z_{min} of 2 mm, he was able to observe perpendicular components of the evoked magnetic field B_z as large as 10 pT, after electrical stimulation. His group has also shown that the detailed waveform of the signal can be modified using chemicals that block certain types of ion channel and thereby affect the inhibitory or excitatory nature of PSCs. This suggests that Okada's technique could have wider applications in neurophysiology. In this paper we will construct a theoretical model of Okada's experiment and use it to show that a SQUID system based upon high temperature superconductors (HTSs) would have considerable advantages over a low T_c system in this application, which Okada calls magnetophysiology. We will describe our progress in developing high T_c magnetophysiology systems and the requirements on SQUID performance.

2. The hippocampal slice model

When an excitatory stimulus occurs at a synapse, a PSC flows into the dendrite and towards the cell body (see Fig. 1a). The associated ion current distribution is similar to that of a current dipole and hence the magnetic field is proportional to $1/z^2$ at large distances. Inhibitory stimuli cause PSCs to flow in the opposite direction. In contrast an AP is a membrane depolarisation wave, with an associated action current (AC) distribution corresponding to two electric dipoles with opposite orientation, travelling along the axon. At large distances the magnetic field is dominated by the current quadrupole moment and hence is proportional to $1/z^3$ Thus at the typical 4 cm measuring distance, the dipolar synaptic field dominates the MEG signal. However, if z approaches the length of the dendrite d (typically 50–1000 μm) the situation may become more complicated.

If we wish to model the magnetic field generated by a structure in the brain, we can approximate the current distribution using a set of current dipoles. Okada's tissue preparation was a slice from the Guineapig hippocampus in which the cell bodies in the CA3 region can be assumed to lie in a single plane with synaptic currents flowing perpendicular to the plane for each cell (Fig. 1b). We assume that the neurons are uniformly distributed throughout the plane so that we can use the Biot–Savart's law in the form:

$$d\mathbf{B} = \frac{\mu_0}{4\pi}\mathbf{Q}''\frac{\mathbf{r}-\mathbf{r}_0}{|\mathbf{r}-\mathbf{r}_0|^3}\,dx\,dz. \quad (1)$$

Here $\mathbf{Q}'' = I_{PSC}d\rho\mathbf{e}_y$ is the dipole density per unit area, I_{PSC} is the typical PSC level, d is the length of the dendrite, ρ is the density of neurons per unit area, $\mathbf{e}_y$ is as unit vector in the y-direction and $\mathbf{r}_0$ is a point in the cell body plane. This expression ignores the magnetic field associated with return

currents, which is only valid when the neurons are in an infinite conducting medium. However Okada considered his tissue bath to be large enough for this approximation to be reasonable.

By integrating over the cell body plane it is possible to calculate the perpendicular component of the magnetic field B_z as a function of position above the slice. This is shown in Fig. 2 for a line directly above the cell body plane. The peak field has been scaled to the typical value observed by Okada et al. of 10 pT at a distance of 2 mm. Using this model we can determine a value of $I_{PSC} = 830$ pA assuming a neuronal density of 5000 mm^{-2} and $d = 200$ μm. This compares favourably with direct measurements of I_{PSC} in this type of neuron [4].

3. SQUID systems for magnetophysiology

The availability of HTS SQUIDs has given rise to the development of "SQUID microscopes" where a small SQUID sensor is brought very close to a specimen at room temperature. These instruments enable magnetic images to be constructed of biological as well as other types of specimen. The

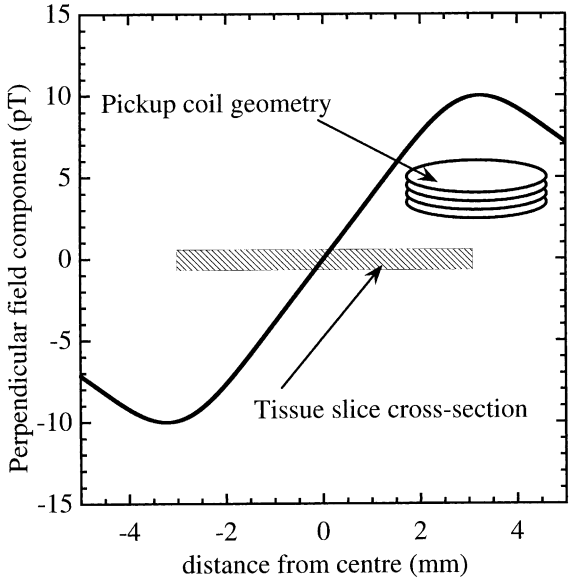

Fig. 2. The variation of B_z with position calculated using the slice model for $z_{min} = 2$ mm. The diameter of Okada's pickup coil is shown for comparison.

Berkeley group [5] have demonstrated that it is possible to bring an HTS SQUID within 15 μm of room temperature using a relatively simple cryostat design which stays cold for almost 24 h using only 1 l of liquid nitrogen. Whilst small z_{min} values can also be achieved with low T_c systems [6], the design is often more complex and it is difficult to keep them cold for as long. In all systems of this type, the z_{min} value is fixed by the size of the SQUID chip, the amount that the vacuum window bends due to the pressure difference across it and its thickness. The larger the SQUID chip, the wider the vacuum window, the more the window bends. Using 50 μm thick single crystal sapphire to make a 5 mm diameter window, the Berkeley group were able to achieve z_{min} values of 60 μm, 30 times closer than the z_{min} value used by Okada.

The key difference between a magnetophysiology system and a SQUID microscope is the tissue chamber. In order to keep cells active in vitro, it is necessary to immerse the tissue in physiological saline solution with an O_2/CO_2 gas mixture bubbling through it. For electrophysiological measurements, stimulating and recording electrodes are inserted into the tissue and voltage responses measured in response to electric current stimulus pulses. In a standard electrophysiology set-up the electrodes are inserted into the tissue from above, using micromanipulators to position them accurately under a microscope. This configuration is particularly convenient for integration into a Berkeley style magnetophysiology system with the sapphire window integrated into the bottom of the tissue chamber. However, it would not be easy to move the source and sensor relative to one another in order to map the magnetic field distribution. In contrast Okada places the tissue beneath the SQUID. Since the SQUID system and the chamber are not connected, it is simple to move one relative to the other in the xy plane by 10 mm in any direction. In this orientation, the electrodes are inserted in the tissue from underneath.

We are engaged in the construction of two SQUID systems directed at this application, one in Cambridge (CAM) and the other at Chalmers (CTH). The CAM system (Fig. 3a) is very closely based upon those developed in Berkeley. The SQUID is mounted on the end of a sapphire rod,

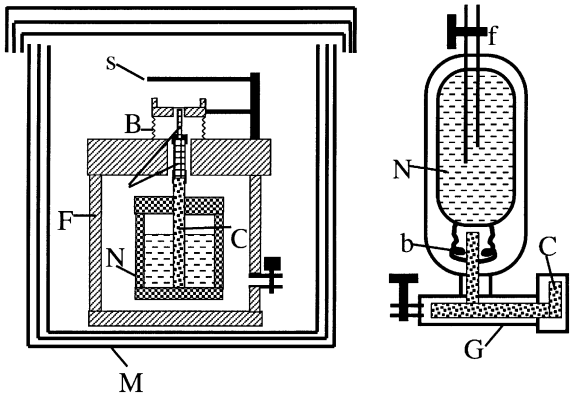

Fig. 3. Schematic diagrams of the magnetophysiology systems being developed at CAM and CTH. The labels are as follows – N: Nitrogen can, C: Copper cold finger, F: Fibreglass casing, M: Magnetic shield, S: Sapphire rod, B: Bellows, s: support for electrodes etc., b: copper braid, f: fill tube, G: Glass SQUID and cold finger chamber. The final supports for SQUID and vacuum window are not shown.

clamped to the surface of a copper liquid nitrogen can. This assembly is wrapped in super-insulation and supported from the lid of an evacuated fibreglass cryostat, so that the SQUID points upwards. The sapphire window assembly is mounted upon brass bellows which allows the SQUID to sample distance to be adjusted. The CAM system is intended to allow magnetophysiology measurements to be carried out simultaneously with a full range of electrophysiology techniques in the standard configuration.

The CTH system (Fig. 3b) is designed so that the SQUID is mounted in a separate chamber from the cryostat containing the vacuum insulated liquid nitrogen can. The SQUID is cooled using an "L" shaped copper cold finger which is encased in a glass vacuum chamber and connected to the nitrogen can using copper braids. With no thermal shielding, the temperature on the end of the cold finger has been measured at 82 K, If we superinsulate the cold finger and pump on the liquid nitrogen can we expect that we will be able to cool the SQUID to 70 K. The vertical section of the cold finger can be rotated to any angle, which allows the system to be used in both the configuration used in the CAM system and in that used by Okada. Thus with the SQUID directed downwards it will be possible to scan the tissue relative to it in order to construct a magnetic field image. Another important difference between the two systems is that it will only be necessary to magnetically shield the SQUID chamber for the CTH system whereas the CAM system will have to be completely shielded.

4. Sensors for magnetophysiology

The detailed anatomical microstructure of a number of regions of the brain, is well known, and the spatial distribution of the current can be modelled. In these cases the key questions that can be answered using magnetophysiology relate to the magnitude and waveform of the neuromagnetic field. In such circumstances, a sensor targeted at this application must be designed so that the maximum magnetic flux from the source can be coupled to it. Thus the approach that we wish to take in our studies is to choose the neuroscience application and optimise the sensor design.

In Okada's microSQUID system, the pick-up coil is 3 mm in diameter, which is well matched to the distribution of magnetic field shown in Fig. 2 with peaks close to the edges of the tissue sample. The 10 pT peak field is a spatial average over the pick-up loop area. Recently we have fabricated 2 mm square directly coupled magnetometers incorporating an HTS SQUID [7]. The best of these devices had magnetic field resolution values in a uniform field of 180 $fT/\sqrt{Hz}$ which is somewhat larger than the 50 $fT/\sqrt{Hz}$ noise level of Okada's system. If we use the 1 kHz bandwidth of Okada's measurements to calculate the equivalent RMS magnetic field noise of Okada's system and a system containing our HTS magnetometer, we find values of 1.6 and 5.7 pT respectively.

We can now use the model of the Guineapig hippocampus, constructed earlier, to compare the expected signal to noise ratio (SNR) for Okada's system with the expected SNR for our sensor, as a function of distance from the tissue. This is shown in Fig. 4, assuming that the magnetometer plane is parallel to the tissue surface and the sensor is positioned in order to maximise the flux coupling. We have assumed that the HTS magnetometer can approach the tissue as close as 50 μm, whilst

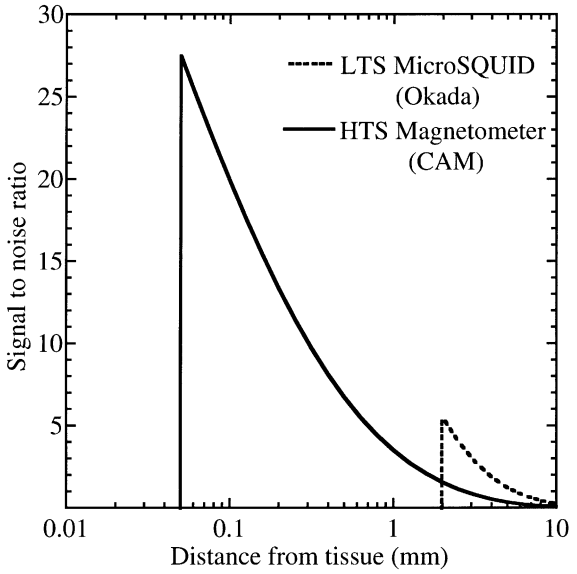

Fig. 4. Variation of signal to noise ratio (SNR) with distance for Okada's system and an HTS magnetometer. Because the HTS magnetometer can get closer, a larger SNR is possible.

Okada's SQUID is limited to 2 mm. As may be observed, the HTS sensor already gives the same SNR at 1 mm and at a working distance of 50 μm, the SNR is a factor of 4 larger. The model we have used has some deficiencies. In particular, the dipolar approximation is probably no longer valid at the shortest distances. There may also be inaccuracies associated with the effect of return currents. It also ignores the averaging of the spatially varying magnetic field distribution across the pick-up area. It is clear that the model needs to be refined, but it is unlikely that these issues will invalidate our conclusion that that the SNR for the HTS system would be significantly larger than that obtained by Okada.

5. Conclusion

In this paper we have described a potential new application for HTS SQUIDs: magnetophysiology. We have constructed a model which enables us to calculate the neuromagnetic field generated by hippocamal brain slices. This model enables us to show that an existing HTS magnetometer would perform better than a low T_c microSQUID system, for this preparation at least. More refined models are required to improve our estimate of the signal to noise ratio. These will also enable us to investigate which other areas of the brain would be suitable for magnetophysiological study. We are in the process of building instruments with which we hope to demonstrate that magnetophysiology experiments can be conducted using HTS SQUIDs. These instruments will be capable, not only of detecting neuromagnetic signals in vitro but of imaging the magnetic field distribution in order to better understand its source. We believe that magnetophysiology will be an important new tool for the neurosciences, allowing non-invasive measurements of PSC levels and will shed new light on the origin of the MEG signal.

Acknowledgements

We gratefully acknowledge discussions with Prof. J. Clarke, Y. Chemla, H. Grossman, Dr. T. Shaw and R. McDermott at Berkeley and Prof. Y.C. Okada and Dr. A. Bartolo in Albequerque. Funding for this project comes from the UK Engineering and Physical Sciences Research Council, the British Royal Society, the Royal Swedish Academy of Sciences and the Swedish Foundation for Strategic Research through its OXIDE programme.

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