Non-invasive monitoring of ionic current flow during development by SQUID magnetometry

S. J. Swithenby

Physics Department, The Open University, Milton Keynes MK6 7AA (England)

Summary. The ionic currents flowing in developing organisms produce weak magnetic fields that can be detected using SQUID magnetometers. The method is non-invasive and dc recording is possible. To date SQUID magnetometers have mainly been used in human studies. The features of the technique are described and the prospects of extending its use to developmental studies are discussed. Feasible instrumental specifications are indicated. A recent SQUID magnetometer investigation of ionic current flow in the developing chick in ovo is summarised as an illustration of the magnetometer method. The paper as a whole argues that magnetometry is a useful alternative or adjunct to electrode-based experiments on the electrophysiology of developing organisms.
Key words. SQUID; magnetometry; ionic current; development; chick.

Introduction

Measurement of the magnetic fields around biological organisms provides a non-invasive method of monitoring their internal electrophysiological activity. The technique is rapidly becoming established in medical research on humans. In this article I will suggest the method can be usefully applied to developmental systems.

At the outset it is important to emphasise that the methodology I will be advocating is unusual in its instrumentation but is firmly embedded within the context of mainstream science. This reminder is necessary because of the chequered history of studies linking magnetism and biology. Charlatans have been attracted to this area since the days before William Gilbert. In his 'de Magnete' published in 1600, Gilbert elegantly dismissed the 'fables and follies' of previous writers who suggested aphrodisiac and exorcising properties for magnets.

Although the claims have become more subtle, there are still many sensational reports on the efficacy of magnetic therapies, often supported by poorly controlled experiments and negligible explanation of mechanisms of action. These reports not only prejudice the reception accorded to other more careful researchers into the *effects* of magnetic fields on biological systems (much of the early work is referenced in Grissett [11]) but also engender scepticism about studies such as I propose – of the magnetic fields *produced* by organism.

Biomagnetic fields are so weak that their accurate measurement has only become possible with the recent development of a type of magnetometer that is ultra-sensitive. The instrument is known as a SQUID (Superconducting Quantum Interference Device) magnetometer. It is a complicated instrument with several unusual features. It offers the prospect of completely non-invasive long-term monitoring, and is capable of dc recording, but it has limited spatial sensitivity.

The article will begin with an estimate of the magnetic field strengths that might accompany development. Then I will introduce the general principles of SQUID magnetometer operation [3, 27, 31]. The aim will be to provide an indication of the instrument's capabilities and limitations in a developmental context. This is a very new area of possible application and illustrations will be given of SQUID magnetometer use in more established areas. To date the only magnetometer based studies of developing systems have been carried out in one institution, The Open University. This work will be described – although preliminary and incomplete it will serve to demonstrate the potential of the magnetometry technique. Finally I will comment on instrumental improvements that could, if realised, be of great benefit to future users.

Feasibility considerations

Throughout this article I will assume that knowledge of the ionic current flow is of interest to those studying development. (This issue has been extensively discussed elsewhere [14, 15, 28, 29].) Certainly considerable effort has gone into charting the phenomenology of ionic currents [15]. The most effective instrument used has been the vibrating-probe electrometer [16], which has good spatial resolution and high sensitivity but is limited to observations of the external current flow created by organisms inhabiting an aqueous environment. Current densities are inferred from vibrating-probe data via assumptions about the conductivity of relevant media. This might be a suspect step in the argument when measuring close to membranes but, ignoring such problems, the current densities found are typically $1-10\ \mu A\ cm^{-2}$. Using these values, we can easily calculate the order of magnitude of the fields created by developing organisms.

Mathematically the currents in and around an organism can be expressed as the sum of a series of current patterns of increasing complexity. The greater the complexity, the more rapidly the field associated with the pattern falls off with distance from the source organism. The simplest electrophysiologically acceptable pattern is a loop of current. Figure 1 shows the field on the axis of a feasible current loop (with 2-mm radius and carrying a current of 0.2 μA) as a function of distance from the loop. Also shown is the peak field associated with the conduction of an action potential down an intact rat spinal cord [34]. From this figure it is clear that an instrument designed

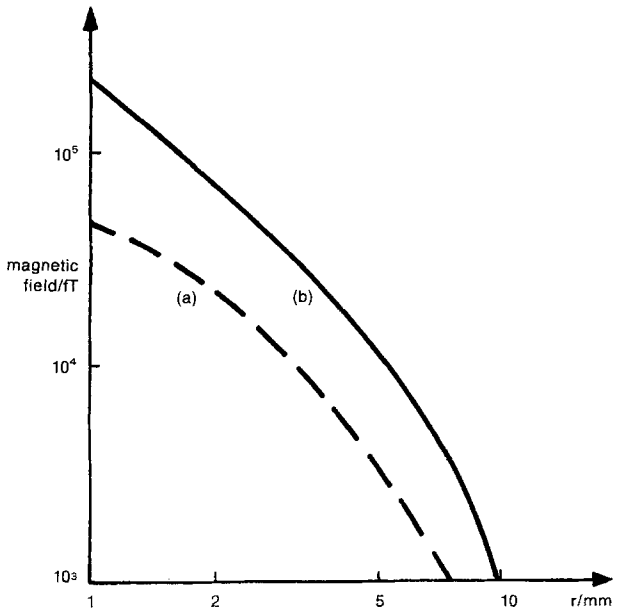

Figure 1. Calculations of the distance dependence of (*a*) the magnetic field on the axis of a physiologically reasonable current loop and (*b*) the peak magnetic field at a distance r from an intact rat spinal cord during the passage of an action potential.

for developmental studies should have a field sensitivity of at least 1000 fT (1 fT = 10^{-15} tesla). In addition, there would be clear advantages if the instrument allowed field measurement close to the organism and had high spatial resolution.

The only magnetometer with sufficient sensitivity for our purposes is the SQUID magnetometer. The table shows its sensitivity relative to both biological and noise sources. As the name implies a SQUID is a superconducting electrical circuit whose behaviour is governed by the macroscopic quantum behaviour of the electrons. In this discussion the SQUID theory is irrelevant. However it is important to understand the performance constraints and these will be summarised below. Fuller accounts of both the theory of device operation and SQUID applications are widely available[3-5, 27, 31-33, 35].

The strengths of the magnetic fields produced by biological and noise sources compared with SQUID magnetometer sensitivities

Source	Magnetic field/fT
Earth	$\sim 5\times10^{10}$ (dc) $\sim 10^7$ (ac)
Power lines	$\sim 3\times10^8$
Urban activity	$\sim 3\times10^8$
Heart	$\sim 10^5$
Skeletal muscle	$\sim 10^5$
Epileptic spike	$\sim 10^3$
Evoked response	$\sim 2\times10^2$
SQUID noise	$\sim$ 10–50 (total) $\sim$ 6 (intrinsic)

SQUID magnetometers

SQUID magnetometers have one or more separate flux detectors. In each of these there is a superconducting pick-up coil whose output is inductively coupled to a SQUID. *The SQUID itself is also coupled to conventional electronics whose output voltage changes linearly with changes in the flux through the pick-up coil.* The system only responds to changes in flux but, unlike a conventional induction coil, such as is used in nmr systems, the response is independent of the rate at which the flux changes. Therefore, in the absence of noise, SQUID sensitivity is independent of frequency. The useful bandwidth is limited by the electronics with most systems operable between dc and about 100 kHz. This good low frequency sensitivity of SQUID system is a considerable advantage but it is important to realise that, to make a dc field measurement, it will be necessary to move either the magnetometer or organism creating the flux change to which the system responds.

Cryogenics. The SQUID and pick-up coil are contained in a liquid helium dewar which is usually made from fibre-glass. Obviously it is advantageous to minimise the distance between the sample, which is at room temperature, and the pick-up coil. Separations of about 10 mm are easy to achieve but thermal contraction, as well as the requirements of mechanical strength, magnetic cleanliness and thermal insulation, pose problems in attempting to achieve substantially lower values. However, with careful design a separation of 1–2 mm may be possible[34]. Liquid helium costs of appropriate dewars are modest, lying in the range \$ 5–\$ 20 per day depending on the source of helium supply and the dewar design.

Sensitivity. Existing commercial SQUID magnetometers have intrinsic sensitivities in the range 5–50 fT $Hz^{-1/2}$. (The bandwith is relevant because the noise is 'white', i.e. its amplitude is proportional to the square root of the bandwidth.) To use this sensitivity it is necessary to reduce the effects of ambient magnetic field noise created by power lines, motors, car movement etc. Two strategies are used. The first is magnetic shielding. Multiple layer magnetically shielded rooms have been constructed with interior noise levels of a few femtotesla but the cost is extremely high and limited, though very effective, use has been made of such facilities[3, 6, 18, 21]. An alternative approach is to use a 'gradiometer' pick-up coil (fig. 2) consisting of several counter-wound coils in series. Gradiometers are insensitive to distant field sources (i.e. noise sources) because the flux contributions from the individual coils sum to zero, but they are sensitive to nearby sources (such as the organism being studied). Most existing gradiometer based systems use second derivative axial coils (fig. 2c): the best have noise levels of $\sim$ 30 fT $Hz^{-1/2}$. One constraint on the use of gradiometers is the desirability of matching the inductances of the pick-up coil and the coil used to couple the signal to the SQUID. Poor matching leads to increased noise levels.

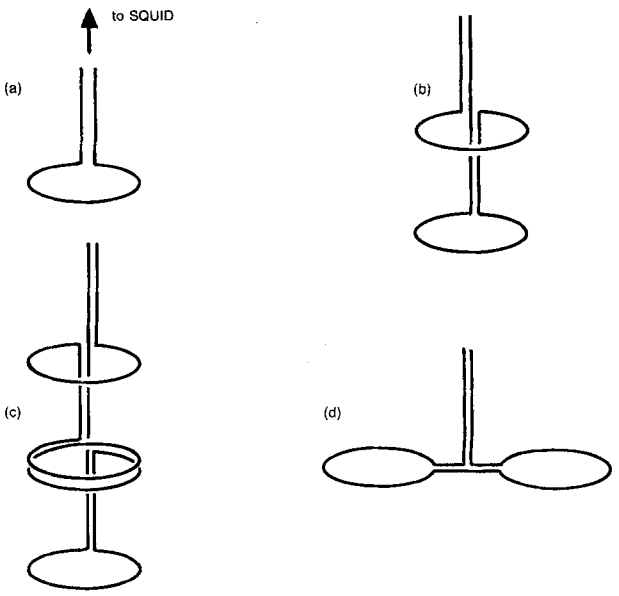

Figure 2. Four alternative pick-up coil systems. Except for (*a*), all are gradiometers and are insensitive to uniform magnetic fields.

Magnetometers designed for study of *small* biological systems will be somewhat different from the present instruments which are designed for human studies. It will be possible to use small (and therefore relatively cheap) magnetic shields. In addition short base-line gradiometers (with good noise rejection properties will be a design option). However the small coils will have less flux sensitivity. A the present time, a noise figure of approximately 30 $fT\,Hz^{-1/2}$ seems to be a reasonable noise specification.

Spatial resolution. In most SQUID biomagnetometers the pick-up coils have a diameter of about 2 cm. This is adequate for the majority of human studies but is not appropriate for research into small organism development. As already noted there is an interplay between sensitivity and coil area but, without departing from conventional pick-up coil-SQUID design, resolution of 1–2 mm should be compatible with adequate noise performance. It may be possible to reduce the resolution further using integrated SQUID pick-up coil arrangements constructed by thin-film deposition (see for example Pegrum et al.[25]). An added advantage of such a strategy is that it would allow efficient (and cheap) production of multiple sensor systems. At the moment multiple sensors are constructed laboriously by individual hand-winding of coils etc. The largest operational instrument, the Gemini system at New York Medical Centre, has 14 measurement channels (many groups are still limited to single-channel magnetometers) and it seems improbable that the number can be increased much further with hand construction techniques. However, with lithographic methods 100 channels seems entirely feasible. A forerunner of the Gemini system is described in Williamson et al.[37].

Source calculation. It is essential to recognise that field resolution does not equate to resolution in the location of the currents. After the fields are measured the current distribution must be calculated using Maxwell's laws – this is known as solving the biomagnetic inverse problem. Without assumption about the form of the sources, the general inverse problem is insoluble. This is an often quoted but sometimes misunderstood result. It doesn't imply that we cannot locate sources; rather it forces us to adopt source models. The inverse problem is then reduced to a search for the parameters of the model. Often a useful model is very simple. For example in magnetoencephalography (meg), just as in electroencephalography (eeg), the brain's activity is associated with one or more current dipoles. (Current elements that drive current through the conducting medium of the brain). Existing biomagnetometers with 2-cm diameter coils are capable of locating small numbers of such dipoles with 2–3 mm accuracy.

It is not clear that such a model would be suitable for developing organisms. Ideally we would like to be able to construct a current density image analogous to NMR or radiographic images. This is very difficult because of poor convergence in the fitting procedures necessary to calculate the image. However some progress has been made using minimum norm methods[13], with which 2-d images have been successfully produced, and an iterative-perturbative algorithm which identifies arbitrarily shaped 3-d current loops[9]. Other novel methods of image creation are currently being researched[24]. In this context it is worth noting that the additional information that can be provided by surface electrodes is very useful in source identification.

In summary, simple current sources should be localisable using magnetometry to better than 1 mm accuracy – the success that will be achieved with more complex source patterns is not known. A recent review volume summarises progress in biomagnetic inverse-problem solution[33].

Applications. Within the broad context of biomagnetism, SQUID systems are used in many areas of study[3,4,32,35]. Most effort is being expended in investigations of human brain activity[36] including for example both clinically relevant work on focal epilepsy[1] and Alzheimer's disease and research-oriented studies of subcortical activity[22]. Other workers direct their attention to the heart[3] (producing the magnetic analog of the electrocardiogram) and the liver[3], where magnetic monitoring of iron overload is possible, as well as other organs such as the eye, lungs, etc.

There has been little work on animal models and few in vitro studies. Wikswo and colleagues[26] have built a series of small toroidal magnetometers and used them in measurements of the magnetic fields associated with the action potential propagating down a single nerve axon. This technique, which provides an alternative to invasive microelectrodes studies, allows long-term monitoring. It

can be used for assessment of peripheral nerve viability in clinical situations. Recently the same group has proposed extending this work through the construction of a miniature SQUID magnetometer with 4 channels, 3-mm diameter pick-up coils and 1–2-mm separation of the 4 K and 300 K environments[34]. This instrument will have a dc recording capability and will be ideal for many developmental studies.

Developmental studies

The only magnetometer measurements directly relevant to biological development and regeneration have been carried out at The Open University. Early work using a magnetometer with a 2.4-cm diameter pick-up coil was concerned with dc ionic current flow associated with fracture repair[10]. This study demonstrated the existence of dc currents of appreciable strength ($\sim$ 10 μA) in both normal subjects and those with fractures (fig. 3). In normal subjects the currents may be associated with the inhomogeneity of muscle fibre membranes; this has been previously observed using electrode methods[2]. Progress in the study has been impeded by a simple practical problem that is relevant to all sensitive dc magnetometer measurements – magnetic contamination. It is essential to avoid using sample preparation techniques – steel scissors, scalpels, etc. – that might lead to the deposition of even the smallest ferromagnetic particle.

I will now describe a recent[19] and continuing study on the fields produced in ovo by the developing chick *Gallus domesticus*. This will illustrate in some detail the way in which a practical study is carried out.

The majority of the measurements were made on 18 normally developing eggs incubated under normal conditions. For each measurement the egg was removed from the incubator and scanned under the magnetometer, with its long axis horizontal, along six equally spaced scan lines (fig. 4). As noted previously, scanning provides the flux variation required to produce a signal. The magnetometer output, is the z-component of magnetic field averaged over the pick-up coil along the scan line. It was sampled at 5-mm intervals and a magnetic field contour map was produced from the data by interpolation (fig. 5).

The data for each map took $\sim$ 3 min to acquire. The signals were constant during this time, indicating negligible cooling of the egg. However, if the egg was allowed to cool for say 30 min, the signal diminished considerably, indicating the metabolic origin of the signals.

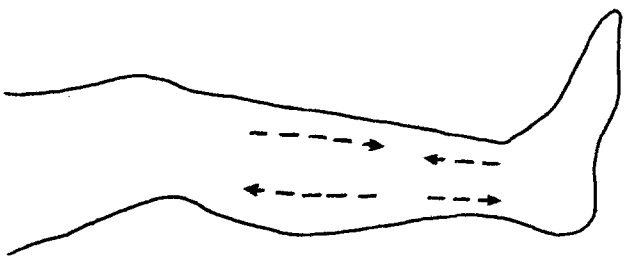

Figure 3. The gross features of the initial current flow in a relaxed normal leg. The current distribution is inferred from field measurements taken on all four sides of the leg. It changes with relaxation.

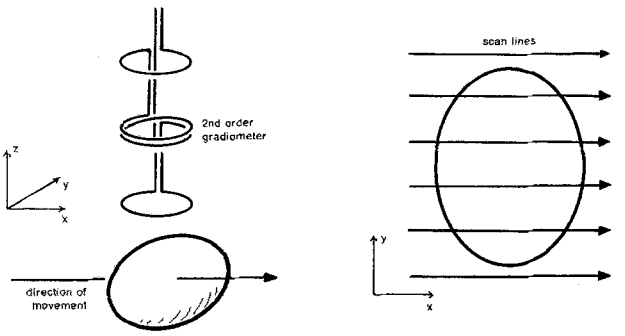

Figure 4. The geometry of the chick experiment.

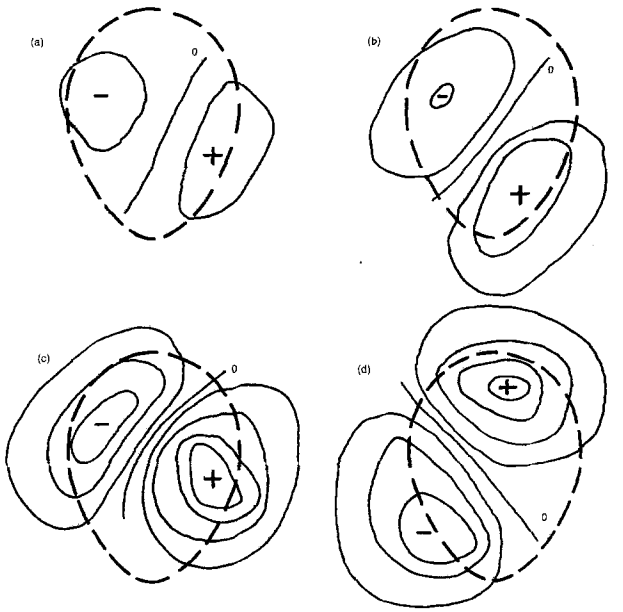

Figure 5. Typical magnetic field contour maps in the early stages of development. The contour lines are at 1000 fT intervals. Incubation times are (*a*) 32 h, (*b*) 45 h, (*c*) 53 h, and (*d*) 67 h. Notice the change in pattern orientation in (*d*). The + and − legends indicate respectively positive and negative z-components of magnetic field.

Figure 6 shows the change in peak signal magnitude with incubation time averaged over the eggs. Typically the signal is first clearly visible at t $\simeq$ 20 h. It then increases in magnitude retaining a similar pattern in most eggs until t $\simeq$ 70 h at which time, within a few hours, there is a marked change in strength and form. Thereafter the signal fluctuates slowly remaining present throughout incubation. No inter-egg consistency is seen after t $\simeq$ 70 h.

In this study the magnetometer that was designed for human studies was used. Its pick-up coils had too large a diameter (2.4 cm) to allow us to resolve more than the gross features of the field pattern and, therefore, it gave us limited information about the underlying source structure. Nevertheless, we have analysed the period of consis-

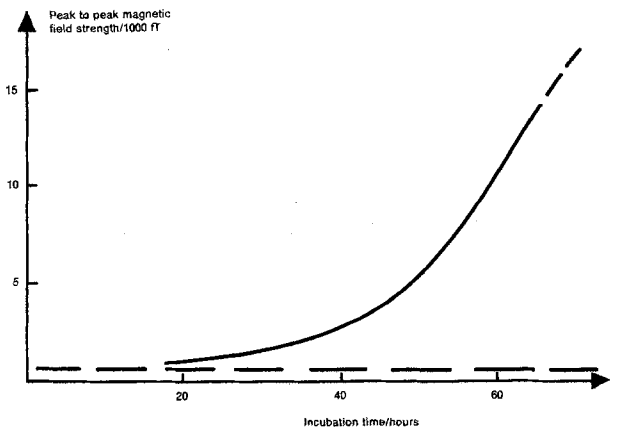

Figure 6. The mean peak-to-peak field in the contour map measured in a plane above the developing chick in ovo as a function of incubation time. The dashed line is the noise level. There is considerable variability in field strength (at least a factor of 2) but signals are typically observable at $t \simeq 20$ h.

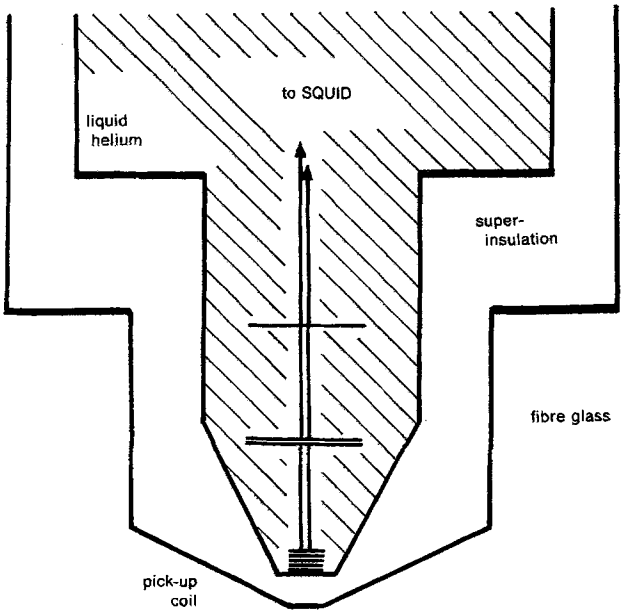

Figure 7. A schematic diagram of the lower part of a recently built miniature magnetometer with a 2-mm radius pick-up coil. The conical design allows free access to the sensitive volume just below the dewar and eases problems in alignment of the inner and outer tails of the dewar.

tent signals before $t \simeq 70$ h (i.e. Hamburger and Hamilton stage 18)[12,20]. The simple bipolar field pattern during this period can be accounted for by a single current-dipole source of strength increasing to $\sim 25\ \mu A\,cm$ located at 7 ± 3 mm from the centre of the egg. The dipole is oriented approximately parallel to the embryo's caudal-capital axis. During this period the embryo is floating on top of the yolk well above the point at which the dipole is located and there is no physiologically reasonable source identifiable with our calculated source. Furthermore, the source strength becomes unreasonably large for a localised dipole. It seems that, to explain the data, we must look to an extended area of source dipoles with a common orientation located nearer the top of the egg.

It would be desirable if we could link our observations with those of other investigators of the electrophysiology of the developing chick but their attentions have been concentrated on slightly earlier developmental stages[17,30]. However, following their work, we suggest that epithelial sheets are the cause of our signals.

This view has been supported by subsequent experiments in which techniques such as windowing, mechanical excision of tissue and pharmacological perturbation have been used.

These experiments, which will be reported in detail in a later paper, were mainly carried out on eggs nearing the end of the period of characteristic bipolar pattern (i.e. approaching 70 h). Removal of the area pellucida containing the embryo and developing amniotic cavity had little effect on the signals, as did the halting of circulation of blood. However, the excision of the area vasculosa membranes (to the radius of the terminal sinus) effectively eliminates the fields. This links the currents to an extra embryonic entoderm function. However attempts to block sodium and calcium pumps have had little effect and the specific function involved remains unclear.

Our conclusions to date are tentative and further work is needed. The most important requirement is better spatial resolution of the fields. A miniature magnetometer has recently been assembled for this purpose[7]. It has a 4-mm diameter sensing coil and is housed in a specially built conical tailed dewar (fig. 7). The design specifies a 5-mm separation between 4 K and 300 K. This has yet to be achieved. Similarly further work will be necessary to reduce the noise level to the expected 30 $fT\,Hz^{-1/2}$. However, a first indication of the capability of this new system is given by simple observations of quasi-dc ionic current flow in regenerating *Acetabularia*[8]. Although, to date, it is only the overall trans-membrane current flow that has been monitored, it is expected that it will soon be possible to produce a local current map. Combining such data with the results of vibrating probe experiments[23] should provide a better understanding of local impedances and hence ion concentrations etc.

The future

Our instrumental goal is to be able to produce a current density image of organisms with a $\sim$ 1-mm resolution and $\sim 0.1\text{-}\mu A\,cm^{-2}$ current density sensitivity. With existing experimental techniques this is highly ambitious. However, even with the more modest performance we can realistically expect, magnetometry can, in conjunction with electrode-based studies provide useful information, particularly on organisms with relatively large dimensions – the chick, giant unicellular algae etc.

Significant technological developments may make the targets indicated above achievable. It is highly probable that, within $\sim$ 2 years, SQUID magnetometers will be

available in the form of a thin-film array (i.e. in an integrated circuit form)[25]. We can expect each SQUID to have millimetre field resolution and low noise performance. Most importantly, the price of manufacture should be low enough that the presently high price of multichannel systems (several hundred thousand dollars) can be reduced.

At a more speculative level the advent of high-temperature superconductors could alter totally the design of experiments. Liquid nitrogen cooling of the pick-up coils (and possible SQUIDs) would allow much greater flexibility in the cryogenic engineering. For example it might be possible to measure more easily the fields on all sides of the organism simultaneously. This would be of tremendous benefit in solving the inverse problem. A second less obvious advantage of having high temperature superconductors is that it would be feasible to build superconducting magnetic shields to create a low noise environment for the experiment – such shields are far more effective than conventional ferromagnetic shields.

A concluding comment. Magnetometry is an unfamiliar experimental technique to most biologists and the amount of information it has so far provided on development is very small. However, it can give new information and is non-invasive. The contribution it makes in the future will be determined partly by instrumental development but, more importantly, by the level of cooperation between the instrumentalists and developmental biologists. The latter group's contribution in defining the problem and interpreting the data will be essential.

1 Barth, D. S., Sutherling, W., Engel, J. Jr, and Beatty, J., Neuromagnetic localization of single and multiple sources underlying epileptiform spikes in the human brain, in: Advances in Epileptology: XVth Epilepsy International Symposium, pp. 379–384. Ed. R. J. Port. Raven Press, New York 1984.

2 Betz, W. J., Caldwell, J. H., Ribchester, R. R., Robinson, K. R., and Stump, R. F., Endogeneous electric field around muscle fibres depends on the $Na^+ - K^+$ pump. Nature *287* (1980) 235–237.

3 Biomagnetism: an Interdisciplinary Approach. Eds S. J. Williamson, G. L. Romani, L. Kaufman and I. Modena. Plenum Press, New York 1983.

4 Biomagnetism: Applications and Theory. Eds H. Weinberg, G. Stroink and T. Katila. Pergamon Press 1985.

5 Buchanan, D. S., Paulson, D., and Williamson, S. J., Instrumentation for clinical applications of neuromagnetism. To appear, in: Advances in Cryogenic Engineering. Ed. R. W. Fast. Plenum, New York 1987.

6 Erne, S. N., Hahlbohm, H. D., and Trontelj, Z., The Berlin magnetically shielded room (BMSR) Section B – Performance, in: Biomagnetism, pp. 79–87. Eds S. N. Erne et al. Walter de Gruyter, Berlin 1981.

7 Freake, S. M., Swithenby, S. J., and Thomas, I., A miniature SQUID magnetometer for the detection of quasi-dc ionic current flow in developing organisms. To be published in The Proceedings of the 6th International Conference on Biomagnetism (Tokyo) 1987.

8 Goodwin, B. C., and Pateromichelakis, S., The role of electrical fields, ions and the cortex in the morphogenesis of *Acetabularia*. Planta *145* (1979) 427–435.

9 Grimes, D. I. F., and Ioannides, A. A., Reconstructing 3-dimensional line current sources from magnetic field data. To be published in: The Proceedings of the 6th International Conference on Biomagnetism (Tokyo) 1987.

10 Grimes, D. I. F., Lennard, R. F., and Swithenby, S. J., Macroscopic ionic currents within the human leg. Phys. Med. Biol. *30* No. 10 (1985) 1101–1112.

11 Grisset, J. D., Biological effects of electric and magnetic fields associated with ELF communication systems. Proc. IEEE Magn. *68* No. 1 (1980) 98–104.

12 Hamburger, V., and Hamilton, H. L., A series of normal stages in the development of the chick. J. Morph. *88* (1951) 49–92.

13 Ilmoniemi, R. J., Hamalainen, M. S., and Knuutila, J., The forward and inverse problems in the spherical model, in: Biomagnetism: Applications and Theory, pp. 278–282. Eds H. Weinberg et al. Pergamon Press 1985.

14 Ionic Currents in Development. Ed. R. Nuccitelli. A. R. Liss Inc., New York 1986.

15 Jaffe, L. F., The role of ionic current in establishing developmental pattern. Phil. Trans. R. Soc. Lond. B. *295* (1981) 553–566.

16 Jaffe, L. F., and Nuccitelli, R., An ultrasensitive vibrating probe for measuring steady extracellular fields. J. cell. Biol. *63* (1974) 614–628.

17 Jaffe, L. F., and Stern, C. D., Strong electrical currents leave the primitive streak regions of chick embryos. Science *206* (1979) 569–571.

18 Kelha, V. O., Pukki, J. M., Peltonen, R. S., Penttinen, A. J., Ilmoniemi, R. J., and Heino, J. J., Design, construction and performance of a large-volume magnetic shield. IEEE Trans. Magn. *MAG-18* (1982) 260–270.

19 Lennard, R. F., The measurement of small ionic currents in living organisms by means of sensitive magnetometry. Ph.D. thesis, Open University, U.K. 1984.

20 Lillie's Development of the Chick – An Introduction to Embryology, 3rd edn. Ed. H. L. Hamilton. Henry Holt and Co., New York 1952.

21 Mager, A., The Berlin magnetically shielded room (BMSR), Section A: Design and Construction, in: Biomagnetism, pp. 51–79. Eds S. N. Erne et al. Walter de Gruyter, Berlin 1981.

22 Okada, Y. C., Kaufman, L., and Williamson, S. J., The hippocampal formation as a source of the slow endogeneous potentials. Electro. clin. Neurophysiol. *55* (1983) 417–426.

23 O'Shea, P., Goodwin, B., and Ridge, I., A vibrating electrode analysis of extracellular ion currents in *Acetabularia Acetabulum* (1988) in press.

24 Palfreyman, N. M., and Ioannides, A. A., Expert techniques in inverse problem solving. To be published in The Proceedings of 6th International Conference on Biomagnetism (Tokyo) 1987.

25 Pegrum, C. M., Hutson, D., Donaldson, G. B., and Tugwell, A., DC SQUIDS with planar input coils. IEEE Trans. Magn. *MAG-21* No. 2 (1985) 1036–1039.

26 Roth, B. J., and Wikswo, J. P. Jr, The magnetic field of a single axon – a comparison of theory and experiment. Biophys. J. *48* (1985) 93–109.

27 SQUID 85: Superconducting Quantum Interference Devices and their Applications. Eds D. Hahlbohm and H. Lubbig. Walter de Gruyter, Berlin 1985.

28 Stern, C. D., Do ionic currents play a role in the control of development? BioEssays *4* (1986) 180–184.

29 Stern, C. D., and Canning, D. R., Gastrulation in birds: a model system for the study of animal morphogenesis. Experientia *44* (1988) 651–657.

30 Stern, C. D., and MacKenzie, D. O., Sodium transport and the control of epiblast polarity in the early chick embryo. J. Embryol. exp. Morph. *77* (1983) 73–98.

31 Swithenby, S. J., SQUIDS and their applications in the measurement of weak magnetic fields. J. Phys. exp. Sci. Instrum. *13* (1980) 801–813.

32 Swithenby, S. J., SQUID magnetometers: uses in medicine. Phys. Technol. *18* (1987) 17–24.

33 The Biomagnetic Inverse Problem; a special issue of Phys. Med. Biol. *32* No. 1 (1987).

34 Wikswo, J. P. Jr, High resolution measurements of biomagnetic fields. To appear, in: Advances in Cryogenic Engineering. Ed. R. W. Fast. Plenum, New York 1987.

35 Williamson, S. J., and Kaufman, L., Biomagnetism. J. Magn. Mag. Mat. *22* (1981) 129–201.

36 Williamson, S. J., and Kaufman, L., Application of SQUID sensors to the investigation of neural activity in the human brain. IEEE Trans. Magn. *MAG-19* No. 3 (1983) 835–844.

37 Williamson, S. J., Pelizzone, M., Okada, Y., and Kaufman, L., Five channel SQUID installation for unshielded neuromagnetic measurements, in: Biomagnetism: Applications and Theory. Eds H. Weinberg et al. Pergamon Press 1985.

0014-4754/88/080673-06$1.50 + 0.20/0
© Birkhäuser Verlag Basel, 1988