

5 INTERACTION MECHANISMS

Many biological processes are affected by electromagnetic fields. Even small changes in internal fields caused by external magnetic fields can affect that biology. Human tissues respond in radically different ways to applied electric and magnetic fields. Electric fields are experienced as a force by electrically charged objects. The electric field at the surface of an object, particularly where the radius is small (for example, at the limit, a point), can be larger than the unperturbed electric field. However, because of the high conductivity of body tissues relative to air, exposure to a static electric field does not produce a significant internal field, but leads to the build up of surface charge on the body. The induced surface charge may be perceived if discharged to a grounded object. In contrast, the magnetic field strength is virtually the same inside the body as outside. Such fields will interact directly with magnetically anisotropic materials and moving charges. These interactions are subtle and difficult to observe in living tissues. Several excellent reviews of the possible physical interactions of static magnetic fields have been published, including Azanza and del Moral (1994); Goodman et al. (1995); Grissom (1995); Frankel and Liburdy (1996); Valberg et al. (1997); Beers et al. (1998); Adair (2000); Zhadin (2001); Binhi (2002); and Binhi and Savin (2003).

Biological effects of static magnetic fields are studied in several specialized fields of research, each with specific objectives and applications. These studies cover a wide range of static field strengths and it is possible that different physical mechanisms are relevant in the different areas, which include:

- animal navigation and the general study of animal behaviour influenced by magnetic fields;
- static magnetic fields as an alleged therapeutic modality, either alone or in conjunction with pharmacological agents;
- static magnetic fields as a component in biological detection of relatively weak environmental and occupational magnetic fields resulting from the distribution and use of direct current electric power; and
- the use of strong magnetic fields for magnetic resonance clinical diagnostic procedures, such as magnetic resonance imaging (MRI), and in chemical analysis and spectroscopy (NMR).

Outline

A number of physical and chemical effects can occur as a result of exposure of living tissues to static magnetic fields. At the level of macromolecules and larger structures, interactions of stationary magnetic fields with biological systems can be characterised as electrodynamic or magnetomechanical in nature. Electrodynamic effects originate through

the interaction of magnetic fields with electrolyte flows, leading to the induction of electrical potentials and currents. Magnetomechanical phenomena include orientation effects on macromolecular assemblies in fields, and the movement of paramagnetic and ferromagnetic molecular species in strong field gradients. Several types of magnetic field interactions have been shown to occur at the atomic and subatomic levels in biological systems. Two such interactions are the nuclear magnetic resonance and the effects on electronic spin states, and their relevance to certain classes of electron transfer reactions in living tissues. These interaction mechanisms will be considered in some detail in this section. Because static electric fields barely penetrate human bodies, they will not be considered further in this chapter.

5.1 Electrodynamic interactions

With some minor exceptions, all chemistry and biology acts exclusively through forces produced by electromagnetic fields acting on electric charges. The science of electromagnetism has had many famous contributors, but it was James Maxwell (1831 - 1879) who placed the laws of electromagnetism into the form in which they are now known. Maxwell's equations are a set of four equations that describe the behaviour of both electric and magnetic fields as well as their interaction with matter. The equations express:

- how electric charges produce electric fields (Gauss' law);
- the absence of magnetic charges (i.e. the impossibility of creating an isolated magnetic pole);
- how currents produce magnetic fields (Ampère's law); and
- how changing magnetic fields produce electric fields (Faraday's law of induction).

The first physical interaction mechanism follows directly from Maxwell's equations (Jackson, 1999).

5.1.1 Magnetic induction of electric fields and currents

The Lorentz force, F , exerted on a charged particle in an electromagnetic field is given by the Lorentz force equation (5.1).

$$F = q(E + v \times B) \quad (5.1)$$

where:

E is the electric field (vector)

B is the magnetic field (vector)

q is the charge of the particle

v is the particle velocity (expressed as a vector).

The electric field is proportional to that part of the force that is independent of its motion. The magnetic field is proportional to the velocity of the charge.

Just as static magnetic fields exert forces on moving electric charges, due to Galilean relativity, changing magnetic fields produce forces on stationary electric charges. The forces on stationary charges are a measure of the electric field. The induced electric field generated by a changing magnetic field can be calculated using the integral form of Faraday's law:

$$\oint_C \bar{E} \cdot d\bar{l} = -\frac{d}{dt} \int_S \bar{B} \cdot d\bar{A} \quad (5.2)$$

where the left-hand side is a line integral over a closed loop C , and the right hand side is the time derivative of a surface integral of the normal component of the magnetic flux through the area S enclosed by C . Equation (5.2) only calculates the average electric field over the loop C , but it is often the only measure available when the actual local field in a complex system can only be estimated with numerical methods that require very detailed knowledge about the fields on the system boundary and its material properties. If we assume that the bulk conductivity of the material is relatively homogeneous, then we can also infer the average induced current by Ohm's law.

Equation (5.2) will register an average electric field when the integral changes with time. If we consider the loop to be of fixed dimensions, this can happen in several different ways:

- the magnetic field itself varies with time. This is the typical situation for many field studies in which a spatially homogenous field modulated, e.g. with a sine wave;
- by motion in a field that has spatial variation. This is, for instance, relevant when transporting a person into or out of a MRI machine that has very strong gradients at the coil entrance; and
- the relative orientation between the loop and the field vector is changed. This is what happens if we rotate the loop in a static field.

A very detailed analysis of these possibilities is available in Ptisyna et al. (1998). The rate of change directly determines the induced field, so that the frequency of the field application, the speed of the motion in a gradient, and the rotation frequency enter directly into the value of the induced fields.

5.1.2 Lorentz force

Ionic currents interact with static magnetic fields as a result of the Lorentz forces exerted on moving charge carriers (equation 5.1). This phenomenon is the physical basis of the Hall effect (see below) in solid-state materials, and it also occurs in several biological processes that involve the flow of electrolytes in an aqueous medium. Examples of such

processes are the ionic currents associated with the flow of blood in the circulatory system, nerve impulse propagation, and visual photo-transduction processes.

5.1.2.1 Flow potentials

A well-studied example of electrodynamic interactions that leads to measurable biological effects is the induction of electrical potentials as a result of blood flow in the presence of a static magnetic field (Tenforde, 2005). These are a direct consequence of the Lorentz force exerted on moving ionic currents, so that blood flowing through a cylindrical vessel of diameter, d , will develop an electrical potential, ψ given by the equation:

$$\psi = |E_i| d = |v| |B| d \sin \theta \quad (5.3)$$

where θ is the angle between B and the velocity vector. That is, the induced electrical potential is proportional to the velocity of the blood flow and to the magnetic field strength. This equation was originally shown by Kolin (1945) to describe the interaction of blood flow with an applied magnetic field, and it forms the theoretical basis for analysing the rate of blood flow using an electromagnetic flow meter (Kolin, 1952).

There have been numerous accounts of flow potentials being recorded in the ECGs of animals and volunteers placed in strong static magnetic fields (see chapters 7.2 and 8.1). These effects are largest in the blood vessels around the heart and in the heart itself (see Tenforde, 2005). It has been suggested that this effect may place a limit on the magnetic field strength that can be safely tolerated by human beings (Schenck, 1992). The possible consequences for human health have been reviewed by Holden (2005).

Several early models of aortic blood flow in magnetic fields relied on an approximate solution of the Navier-Stokes equation describing the dynamic properties of an electrically conductive fluid flowing in the presence of a strong magnetic field (Hartmann, 1937; Hartmann & Lazarus, 1937). The results of these theoretical calculations indicated that static magnetic fields should produce only small magnetohydrodynamic effects on blood flow in the aorta at field levels up to 2 T (Belousova, 1965; Vardanyan, 1973; Abashin & Yevtushenko, 1974; Sud et al., 1978; Kumar, 1978; Tenforde et al., 1983; Chen & Saha, 1985; Sud & Sekhon, 1989). An exact solution of the Navier-Stokes equation was later obtained by Keltner et al. (1990), and led to a similar conclusion. All of these models made the simplifying assumption that the wall of the aorta is not electrically conductive.

Kinouchi et al. (1996) developed a theoretical model assuming finite conductivity of the arterial wall. In this model, a complete solution of the Navier-Stokes equation for aortic blood flow was obtained by a

finite element analysis method for static magnetic fields of arbitrarily high intensity under the condition that the wall of the aortic vessel is electrically conductive. This model was used to obtain quantitative estimates as a function of the applied magnetic field of the magnetically-induced fields and currents in the aorta, magnetohydrodynamic slowing of the aortic blood flow rate and the leakage currents passing from the aorta into the thoracic region, including those present at the sino-atrial pacemaker node of the heart. In a 5 T field, the predicted current density at the sino-atrial node was about 110 - 120 mA m⁻², rising to about 220 mA m⁻² at 10 T and 300 mA m⁻² at 15 T. Theoretically, the greatest effects should occur for flow in long blood vessels orthogonal to the static magnetic field, while no effect should be seen for flow aligned with the field. Orientation of the patient with respect to the magnetic field may be a consideration for any bio-effects, but this has not been considered in detail.

5.1.2.2 A theoretical study of the possible effects of flow potentials on the heart

Holden (2005) assessed the effects of the electric fields and currents induced by the flow potentials on cardiac function using virtual cardiac tissues – computational models of cardiac electrophysiology. These models are used to understand the normal and pathological electrophysiology of the heart and how this can be modified by pharmacological intervention. The author noted that, although the flow potential generated by blood flow in the aorta will be the largest, a greater fraction of the smaller potentials generated in blood vessels on or in the myocardium of the heart have less distance over which to decay, and so may have the largest effect. Three possibilities were considered, including changing the rate of excitation of the heart by acting on the sino-atrial pacemaker tissues, inducing the ectopic initiation of activity at sites that are not normally endogenously active, and triggering arrhythmias by altering the pattern of action potential propagation through the ventricular myocardium.

Electrical currents generated by flow potentials will have either a depolarising or hyperpolarising effect on myocardial tissue, depending on the orientation of the induced current relative to the myocardial tissue. Holden (2005) noted that, in the sinoatrial node, a greater fraction of external current would flow into the peripheral cells, whereas the pacemaker function resides primarily in cells located at the centre. This possibly may contribute to the lack of any effect of 8 T static fields on heart rate {Chakeres, 2003 736 /id /ft "; see below"}, although a change in rate would, however, be considered benign. Such current flow may also initiate ectopic activity, if action potentials are excited in a sufficiently large volume of myocardial cells. This could be induced by relatively small changes in membrane potential, if the cell parameters are very close

to a critical value (one that produces an early after-depolarisation during an action potential). However, the initiation of activity at an ectopic focus would be suppressed by a higher rate of activity driven by the sinoatrial node. In addition, ectopic beats are also considered relatively benign. These two effects are thought to have thresholds in excess of 8 T.

The situation is more complex with regard to ventricular fibrillation. The flow potentials induced in coronary arteries and branches (but not those induced by the aorta) will have opposite polarities on opposite sides of the left ventricle. This would increase the electrical heterogeneity of the ventricle and so may enhance or establish spatial gradients in action potential duration between different parts of the ventricle. This is likely to increase the probability of the initiation of re-entrant arrhythmias, which can be lethal. However, the author noted that such re-entrant arrhythmias are very rare events, so that even a large increase in their probability leaves them remaining very unlikely in an individual during an exposure period of up to a few hours. Nevertheless, a more precise indication of the risk, and threshold, which Holden (2005) notes is lower than that for pacemaker modulation and ectopic beat induction, would be of value. This is especially the case in people that are more susceptible to re-entrant arrhythmias, such as people with enlarged (hypertrophic cardiomyopathy) or damaged (postinfarct) hearts, and carriers of some rare inherited disorders in repolarisation, including the long QT syndrome. Similar simulations in non-homogeneous magnetic fields are yet to be completed.

5.1.3 Magnetohydrodynamic model

Flow-induced electric currents also act through magnetohydrodynamic (MHD) forces to produce a retarding force on blood flow. It has been estimated that there is a 5% reduction in humans in the flow rate at 10 T, rising to 10% at 15 T (Kinouchi et al., 1996), compared to Keltner's estimate (Keltner et al., 1990) of 0.2% pressure change at 10 T for worst-case conditions (magnetic field orthogonal to flow in long blood vessels). Kangarlu et al. (1999) observed no blood pressure changes in dogs exposed to 8 T fields for 3 hours. In contrast, studies of blood pressure changes in volunteers indicated that systolic pressure rose by about 4 mm Hg in an 8 T static field, which is consistent with a haemodynamic compensation for a magnetohydrodynamic reduction in blood flow (Chakeres & de Vocht, 2005), see section 8.1.2.2.1.

Schenck (2005) has suggested that the mild sensations of vertigo and nausea often experienced by MRI patients might be related to a magnetic interaction with the vestibular apparatus of the inner ear. There are three semicircular canals in this structure that are roughly orthogonal to one another. Each is sensitive to a different component of the angular

acceleration of the head. Each of these canals is filled with a conducting fluid called the endolymph and contains structures at one end referred to as neuromast organs. These consist of sensory (hair) cells and supporting cells covered by a gelatinous cupula. When the head undergoes angular acceleration, the inertia of the endolymph produces a force on the cupulas, which are slightly deflected by it. This transfers to the hair cells in the neuromast organs and initiates a signal that is eventually interpreted within the central nervous system as a head motion. Any excitation of hair cells by the magnetic field would be perceived as an extraneous head rotation that would not correspond to other sensory inputs. A field-induced excitation could result from direct depolarization of sensory cells or from diamagnetic anisotropy in the cupula, which would produce torque and deflection of this structure when the head was turned. Another possibility (Schenck, 1992) is that the changing magnetic flux through the semicircular canals when the head is turned leads to an additional force, of magnetohydrodynamic origin, on the endolymphatic fluid.

The mild vertigo and nausea is analogous to similar symptoms associated with motion sickness. According to the conflict hypothesis (Brandt, 2003) motion sickness is the consequence of discordant inputs to the brain information about the position and motion of the body from the vestibular and the visual systems, and from other sensory sources. Further work is necessary to determine if these field-related sensory effects can be explained by magnetohydrodynamic forces acting on the semicircular canals or by other induced current effects.

5.2 Magnetomechanical interactions

There are two basic mechanisms through which static magnetic fields exert mechanical forces and torques on objects. In the first type of magnetomechanical interaction, rotational motion of a substance occurs in a uniform field until it achieves a minimum energy state. The second mechanism involves the translational force exerted on a paramagnetic or ferromagnetic substance placed in a magnetic field gradient, although in theory the only requirement is that the object has a different magnetic susceptibility to its surroundings.

Other less understood mechanisms are related to rotations and vibrations of ions and charged molecules in static magnetic fields. These mechanisms have not been established.

Another important aspect of magnetomechanical interactions with biological systems are the forces exerted by the geomagnetic field on magnetotactic bacteria and in the tissue structures in various organisms that contain deposits of biogenic magnetite (see section 5.4).

5.2.1 Magnetomechanics (torque on magnetic dipole moment)

Macromolecules and structurally ordered molecular assemblies with a high degree of magnetic anisotropy will experience a torque in a uniform magnetic field and rotate until they reach an equilibrium orientation that represents a minimum energy state.

A magnetic dipole with moment \vec{m} in an external magnetic field \vec{B} experiences a torque

$$\vec{N} = \vec{m} \times \vec{B} \quad (5.4)$$

and the potential energy associated with the system is:

$$U = -\vec{m} \cdot \vec{B} \quad (5.5)$$

Hence, the effect of the field is a tendency to rotate the dipole towards alignment with the field. This is the basis for various interaction mechanisms. Note that this does not occur for magnetic dipoles that are formed in isotropic diamagnetic or paramagnetic materials in response to an applied magnetic field, since their magnetic moments would be aligned parallel (or anti-parallel) with the local field. If we have a material with intrinsic magnetization or with anisotropic susceptibility, then there is a possibility for a physical mechanism (see section 5.2.3 on anisotropic diamagnetism).

In living systems, the effect of thermal noise will tend to randomize the dipole's orientation. The energy U has to be compared to $k_B T$ (where k_B is Boltzmann's constant) for typical temperatures of living systems ($T \sim 310$ K). For protons with a nuclear magneton of magnetic moment ($\mu_B = e\hbar / 2m_e$), the comparison leaves a very slight alignment even at high (> 1 T) fields, although it is large enough to be technologically useful for MRI.

An example of an intact cell that can be oriented magnetically is the deoxygenated sickle erythrocyte. It has been shown that these cells, in which the deoxygenated haemoglobin is paramagnetic, will align in a 0.35 T static field with the long axis of the sickle cell oriented perpendicular to the magnetic flux lines (Murayama, 1965). Another example of systems that overcome the thermal drive to isotropy is that of magnetic moments created by diamagnetic anisotropy in relatively large structures (see section 5.2.3).

5.2.2 Magnetophoresis (force on magnetic dipole moment)

The second mechanism through which static magnetic fields exert mechanical forces and torques on objects involves a translational force. A

magnetic dipole (\vec{m}) in a static gradient magnetic field experiences a (lowest order) force of:

$$F = (m \cdot \nabla)B \quad (5.6)$$

The magnetic dipole can be a permanent dipole or its magnetization can be induced by the field itself. An example of the latter is diamagnetic levitation in which the force is sufficiently large to oppose the gravitational pull (Beaugnon & Tournier, 1991; Valles, Jr. et al., 1997). The magnetic moment of an object of volume V and magnetic susceptibility χ in a field B is:

$$m = \chi V B / \mu_0,$$

where μ_0 is the permeability of vacuum. To balance the force of gravity, ($g\rho V$) we need $B \nabla B > 1000 \text{ T}^2 \text{ m}^{-1}$ for typical tissue parameters.

This effect is possible for ferromagnetic materials in high gradients, such as those encountered in magnetic resonance imaging. A realistic example (Kangarlu & Robitaille, 2000) shows how typical MRI conditions can accelerate a steel wrench to over 40 m/s^2 . In addition, significant magnetic forces are exerted on many types of implanted medical devices, including aneurysm clips, dental amalgam, prostheses, and pacemaker cases (Tenforde & Budinger, 1986; ASTM, 2003a; ASTM, 2003b).

Some alleged therapeutic applications of magnets claim that strong gradients are required for efficacy (McLean et al., 1995), with a threshold gradient observed somewhere in the region of 1 T m^{-1} (Cavopol et al., 1995). The corresponding threshold force on a Bohr magneton is approximately 10^{-23} N . As a comparison, the electric field required to apply this force on a unit charge is $E = 1.7 \times 10^{-4} \text{ V m}^{-1}$. This is a very small field, but it is in within range of another threshold $E = 4 \times 10^{-4} \text{ V m}^{-1}$ suggested by other experimental studies (Blank & Soo, 1992; Blank & Soo, 1996). The mechanism of magnetophoresis of diamagnetic materials is the only proposed mechanism for gradient specific effects, but it probably does not provide an explanation of the experimental evidence at this relatively weak end of exposures.

Experiments on the rate of myosin phosphorylation in a gradient magnetic field (Engström et al., 2002) suggest that a combination of field and gradient are required to explain the mechanism producing the effect on this biochemical enzyme system.

The forces exerted on paramagnetic and ferromagnetic substances by strong static magnetic field gradients provide the physical basis for a number of useful biological and biochemical processes (ICNIRP, 2003). Examples of the application of magnetic forces include the targeting of

drugs encapsulated in magnetic microcarriers (Widder et al., 1982), the separation of deoxygenated erythrocytes from whole blood (Melville, 1975; Paul et al., 1978), the separation of antibody-secreting cells from a suspension of bone marrow cells (Poynton et al., 1983), and the removal of micro-organisms from water (De Latour, 1973; Kurinobu & Uchiyama, 1982). It has also been observed that strong magnetic field gradients can influence the distribution of deoxygenated, paramagnetic erythrocytes in a flowing suspension of blood cells (Shiga et al., 1993). It has been suggested (Ichioka et al., 2000) that this effect could retard the rate of blood flow when the product of the flux density and the field gradient exceeds $100 \text{ T}^2 \text{ m}^{-1}$.

5.2.3 Anisotropic diamagnetism

If a material has anisotropic diamagnetic susceptibility, then a static magnetic field will apply a torque on the system, since the orientations parallel and perpendicular become differentially magnetized. Orientation with respect to the field becomes energetically differentiated and we have the basis for a physical transduction mechanism (Maret & Dransfeld, 1977). The energy of a cylindrical molecule with magnetic susceptibility χ_p and parallel and perpendicular to the cylinder axis, respectively, is:

$$E = -VB^2(\chi_p - \chi_q)/2\mu_0 \quad (5.7)$$

where V is the molecular volume.

Substantial fields are typically needed to take advantage of this mechanism, and large, elongated, structured molecules do better in the competition with thermal noise. For example, a $5 \mu\text{m}$ long microtubule is estimated to be completely aligned by a magnetic field in the 10 T range (Bras et al., 1998). When material is organized so that the diamagnetic anisotropies align over some volume, larger induced magnetic moments can be achieved. This effect is sometimes called superdiamagnetism (Braganza et al., 1984).

This mechanism is the basis for some detailed models of effects in lipid bilayers (Helfrich, 1973; Gaffney & McConnel, 1974; Tenforde & Liburdy, 1988), subsequent effects on calcium liberation (del Moral & Azanza, 1992; Azanza & del Moral, 1994), and an explanation of how mitotic structures may be affected by large fields (Denegre et al., 1998; Valles, Jr. et al., 2002), resulting in abnormal embryonic development.

5.3 Radical recombination rates

Spin-correlated radical pair chemistry has long been a consideration for magnetic field effects in chemistry and biology. Several classes of organic chemical reactions can be influenced by static magnetic

fields in the range of 10 - 100 mT as a result of effects on the electronic spin states of the reaction intermediates (Schulten, 1982; McLauchlan, 1989; Cozens & Scaiano, 1993; Grissom, 1995; Hore, 2005). A spin-correlated radical pair may recombine and prevent the formation of reaction product if two conditions are met: 1) the pair, formed in a triplet state, must be converted into a singlet state by some mechanism and 2) the radicals must physically meet again in order to recombine. Step 1, the singlet-triplet interconversion, is the step that can be magnetic field sensitive. The probability of having a re-encounter is dependent on how constrained the diffusive motion of the two radicals is. There are several mechanisms outlined within this framework, for example, by McLauchlan and Steiner (1991).

If the two radicals have different g-factors, they will differentially precess and oscillate in and out of triplet and singlet states, allowing for a high rate of re-conversion in the short interval after the pair generation when the re-encounter probability is high. This process becomes dominant at high fields (> 1 T) and is generally referred to as the Δg - mechanism.

At intermediate field strengths (down to the mT range), spin mixing due to hyperfine interactions dominates the singlet-triplet interconversion. The rate of this type of spin conversion is higher when the involved nuclear states are significantly different. The magnetic field has an effect in this regime because it separates the degenerate energy levels of the triplet state, leading to enhanced spin conversion as the T_{-1} state experiences an enhanced ability to mix into the singlet state. At higher field strengths the T_{+1} states become decoupled from any interaction with the singlet state and a reduction in the interconversion rate occurs. This mechanism is fairly well understood and is experimentally supported by detailed experiments (Harkins & Grissom, 1995).

There is also a low field effect based on the fact that the selection rules of hyperfine-induced mixing are more restrictive in zero fields and that one might see a reduction in spin conversion rates for low fields (McLauchlan & Steiner, 1991). Given a reaction environment that imposes spatial constraints on the radical pair diffusion so that long recombination times can be possible, this free radical low field effect is predicted to achieve significant responses to magnetic fields in the μ T region (Timmel et al., 1998; Till et al., 1998). Further structure in the response to varying magnetic field amplitude has been predicted if anisotropic hyperfine structures are considered (Timmel et al., 2001).

It should be noted that the radical pair mechanism requires the two radicals to be spin-correlated or geminate (twins). If they are not statistically correlated with each other, then a magnetic field will still rotate the spin angular momentum, but no coherent change in

recombination rates will occur. This applies to freely diffusing radicals, and it is important to exclude these chemical species from consideration as a magnetic field target (Brocklehurst & McLauchlan, 1996).

Since the radicals stay spin-correlated for a relatively short time, it has been argued that an effect of low frequency magnetic fields should be equivalent to a static field with appropriate amplitude. However, this may not be true if the dynamics of the biological system responding to the time-varying field has any frequency specificity in the appropriate range (Walleczek, 1995; Eichwald & Walleczek, 1998). The property of timescale of the transductive mechanism can be investigated with appropriate experiments (Engström, 1997; Engström & Fitzsimmons, 1999).

Radical pair magnetic field effects have been used as a tool to study enzyme reactions, in part because more than 60 enzymes use radicals or other paramagnetic molecules as reaction intermediates. It has been established (Hore, 2005) that two (non-mammalian) enzyme reactions are magnetic-field sensitive under appropriate, non-physiological, conditions: 1) the conversion of ethanolamine to acetaldehyde by the bacterial enzyme ethanolamine ammonia lyase (Harkins & Grissom, 1994) and 2) the reduction of hydrogen peroxide by horseradish peroxidase (Taraban & Leshina, 1997). Changes in catalytic rates of up to 30% were found for fields of up to 0.3 T. Although there remain biological systems worthy of further investigation, there is, based on the evidence at present, no strong likelihood of major effects of physiological consequence on cellular functions or of long-term mutagenic effects arising from magnetic-field induced changes in free radical concentrations or fluxes (Hore, 2005).

5.4 Biogenic magnetite

Biogenic magnetite is the basis of a well-documented mechanism explaining how some bacteria can use the magnetic field to an evolutionary advantage (Blakemore, 1975). A chain of magnetosomes provides a large enough magnetic moment that the whole organism orients and swims along geomagnetic flux lines (magnetotaxis), providing a reliable source of direction for swimming up or down as this bacterium's circumstances require.

The large magnetic moment associated with a magnetite grain results in the potential energy for rotation in a magnetic field having a magnitude comparable to kT at biological temperatures.

Kirschvink et al. (2001) reviewed the development of magnetite-based magnetoreception and argued that a highly evolved sensory system capable of explaining the observed sensitivities to very small variations in the geomagnetic field should be expected (Fischer et al., 2001; Phillips et al., 2002). An interesting requirement for high-resolution observation of

the magnetic vector orientation is an equally sensitive measurement of the gravitational vector, as well as integration/comparison of these two senses.

Magnetite-based mechanisms are modelled in bio-electromagnetic research (Phillips, 1996; Deutschlander et al., 1999b; Ritz et al., 2000) and there are data in various forms for several different animal models (Beason & Semm, 1996; Brassart et al., 1999; Deutschlander et al., 1999a; Lohmann & Johnsen, 2000; Hanzlik et al., 2000; Phillips et al., 2001; Wiltshcko & Wiltshcko, 2002).

5.4.1 *Single-domain crystals*

Single domain magnetite crystals can only be magnetized along one axis (with positive or negative polarity), and the crystal maintains the magnetization, unlike superparamagnetic magnetite (see below). Single domain magnetite or greigite are the elements of magnetotactic bacteria. It has been suggested that these are functional components of higher magnetosensitive animals. Remagnetization experiments provide good reasons to believe that permanent ferromagnets are involved in the physical transduction (Beason et al., 1997; Munro et al., 1997). Physical models utilizing single domain crystals have been discussed in the literature (Kirschvink et al., 1992).

Edmonds (1996) proposed a sensitive biological magnetic compass by examining the behaviour of a cluster of needle-shaped magnetite crystals in a nematic fluid. The argument is that this system would be able, given enough crystals in the cluster, to respond to the orientation of the magnetic field with relatively high resolution and that useful detection could be achieved optically.

5.4.2 *Superparamagnetic magnetite*

Superparamagnetism is a phenomenon by which magnetic materials may exhibit behaviour similar to paramagnetism at temperatures below the Curie or the Neel temperature. Superparamagnetic magnetite grains are too small to have a stable magnetic moment impressed, but they do respond to an externally applied field. Clusters (1 - 3 μm in diameter) of superparamagnetic nanocrystals (2 - 5 nm in diameter) have been reported in the upper beak of homing pigeons (Hanzlik et al., 2000; Winklhofer et al., 2001). Single domain features were ruled out in these studies.

5.4.3 *Other ferromagnetic inclusions*

There are suggestions of possibilities other than magnetite for ferromagnetic inclusions in bacterial and archaeal cells (Vainshtein et al., 2002). These reported structures were detected by magnetophoresis in a

tesla-level field. The structures did not show the crystalline signatures of magnetite.

5.4.4 Local amplification due to ferromagnetic material

It is conceivable that magnetotransduction could occur in the immediate vicinity of a magnetite grain, if this would provide a local amplification of the applied field. If a particle has magnetic permeability larger than one, it will produce a locally enhanced field and this secondary field could be detected. Another possibility is that a permanently magnetized single domain grain could be rotated by the magnetic field and 'shine' its own relatively large local field onto a nearby magnetic field sensitive structure.

5.5 Mechanistic co-factors and other mechanisms

There are co-factors in some experimental work of static and low frequency magnetic field studies that might provide clues about low level mechanisms. These are discussed below.

5.5.1 Light as a co-factor

One recurring theme is light sensitive magnetic field detection (Ritz et al., 2002). It has been shown that wavelength specific effects occur in avian and reptile magnetic navigation (Deutschlander et al., 1999b) and in magnetic field detection (Deutschlander et al., 1999a). A model is proposed in salamanders in which two separate and antagonistic magnetic field sensitive systems are activated by short and long-wavelength light (Phillips et al., 2001).

Animal models are used to investigate the relation between magnetic field detection and light by forming hypotheses that can be tested by training, and later testing, behavioural responses in various light conditions varying with respect to wavelength (Deutschlander et al., 1999a) and polarization (Able & Able, 1993). The presence of light is also required in a snail behavioural model in which nociceptive responses are modulated only by magnetic fields (Prato et al., 1997).

It is not known whether the light dependent part of the biological mechanism at work is integrated with the magnetic field transduction. It is uncommon in sensory physiology for two independent detectors to become tightly integrated, but one model for the avian magnetic field detection embeds the detection organ in the bird's eye (Ritz et al., 2000). It could also be that light is enabling a physical detection mechanism, either on a behavioural level, or directly, as suggested by Leask (1977).

5.5.2 State dependence

State/activation dependent factors have been theoretically examined in a model of free radical responses in enzyme systems (Eichwald & Walleczek, 1996). It has been experimentally observed that the sign of the response of Na-K-ATPase depends upon its activation state (Blank & Soo, 1996).

5.6 Constraints on physical detection

For either the direct magnetic fields or the magnetically induced electric fields to affect the biology of systems, the interactions with such systems must generally be larger than the interactions with endogenous physiological and thermal noise. The disruptive effects of thermal noise puts limits on what signals can be detected in simple biological systems (Adair, 1991; Adair, 2000). Much work on the possible lower limits of detection has focused on energetic comparisons to the average thermal energy of the environment encountered by any detection mechanism operating in a living biological setting. It should however be noted that the magnetic interactions involved in the radical pair mechanism are weak compared to thermal energy (Hore, 2005).

5.7 Conclusions

It has been shown in this chapter that the following three classes of physical interactions of static magnetic fields with biological systems are well established on the basis of experimental data:

- (1) electrodynamic interactions with ionic conduction currents;
- (2) magnetomechanical effects, including the orientation of magnetically anisotropic structures in uniform fields and the translation of paramagnetic and ferromagnetic materials in magnetic field gradients; and
- (3) effects on electronic spin states of reaction intermediates.

Forces and torques on both endogenous and exogenous metallic objects are the interaction mechanism of most concern. The induction of electric fields and currents in tissue is also of concern. Other interaction mechanisms do not appear to be of concern at this stage. None of the mechanisms discussed to date would seem to indicate differences in effects from acute or chronic exposures, although no suitable epidemiological studies are available in this regard.