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# Quantum effects in biology: Bird navigation

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**Abstract**

Birds possess a physiological magnetic compass, enabling them to make correct directional choices during their migratory flights. The biophysical basis of this compass remains unknown. One of the two major hypotheses postulates that birds use a light-induced radical pair reaction involving coherent spin evolution of two electrons as the foundation of their magnetic compass sensor. This hypothesis has received significant attention during the past decade. Here, we review the growing body of chemical, biophysical, behavioral, and neurobiological evidence suggesting that this quantum-based mechanism may indeed form the basis of the avian magnetic compass.

*Keywords:* radical pair reactions, avian magnetic compass, cryptochrome, radio frequency magnetic field effects

## 1. Introduction

Bird navigation is a complex enterprise, requiring birds to make repeated and varying orientation decisions based on directional and positional information. Birds are aided by multiple physiological compass systems, among them a physiological magnetic compass. The existence of a magnetic compass was discovered in orientation experiments with birds in cages by Wolfgang Wiltschko in the late 1960's. We refer to his contribution as a speaker of the Solvay Congress for more details on the experimental set-up and properties of the avian magnetic compass [1]. In the 1970's, studies indicated that weak magnetic fields can influence chemical processes involving photoactivated radical pair intermediates, i.e. a transient pair of molecules with an unpaired electron spin each. The underlying mechanism was shown to be based on the effects of magnetic fields on the electron spin evolution in each of the radical pairs and investigation of such effects open the now mature field of spin chemistry. It was Klaus Schulten who first suggested that this radical pair mechanism might operate in the compass of migratory birds [2].

The suggestion that bird navigation was aided by the exploitation of coherent quantum effects appeared at first sight rather far fetched and for many years, evidence supporting this idea was sparse. Its main impact was to trigger research into light effects on the magnetic compass of birds. If a photoactivated radical pair mechanism were to underlie the magnetic compass, one would expect that light was a pre-requisite for proper operation of the avian magnetic compass. Indeed, light effects were observed on the magnetic compass of birds. While the varied studies of light effects do not conform to a simple picture and some studies are inconsistent with others, overall, these studies suggest that the magnetic compass operates best under blue and green light and is disrupted under yellow and red light with a fairly sharp transition between orientation and disorientation around 570 nm.

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One reason for skepticism towards the radical pair hypothesis was the lack of a known photoreceptor molecule in animals that can undergo radical pair reactions. This situation changed when cryptochromes, a class of blue-green light photoreceptor molecules were discovered in 1998. Cryptochromes, unlike the opsin-based photoreceptor molecules known in birds, transfer electrons upon light absorption and thereby create potentially magnetosensitive radical pair intermediates. Because cryptochromes were discovered in phylogenetically disparate organisms, such as fruit flies, mice, and plants, it appeared reasonable to suggest that cryptochromes might also exist in birds [3] and to re-introduce the radical pair hypothesis to the biological community. In the decade following, the radical pair hypothesis has received renewed attention that led to several key discoveries, among them the discovery of a brain area linked to the eye that is active during magnetic orientation and that needs to be intact for magnetic compass orientation [4], the experimental demonstration of earth-strength magnetic field effects on a radical pair reaction [5], the demonstration of disruptive effects of radio-frequency oscillating fields on a magnetic compass [6] and, finally, several reports of magnetic field effects on cryptochrome-mediated responses. There exist several excellent and up-to-date reviews covering the radical pair mechanism and the magnetic compass of birds. Each of these reviews focuses on particular requirements and sets of studies, e.g. the light dependence of the avian magnetic compass [7], the chemical requirements of a radical pair mechanism in the context of the avian magnetic compass [8], the behavioral and neurophysiological evidence supporting the radical pair and alternative hypotheses [9], and the possible role of cryptochromes [10, 11]. A more speculative perspective article highlights potential new research avenues from the radical pair mechanism [12]. Here, we aim to provide a broad perspective of the radical pair mechanism in the context of avian navigation rather than focusing on any one particular aspect. After an introduction of the radical pair mechanism, we will discuss behavioral, neurobiological, biophysical, and other evidence supporting a role of the radical pair mechanism in bird navigation. We hope to show that the radical pair mechanism is not only a viable possibility, but in fact, arguably, the most promising hypothesis for the mechanism underlying the magnetic compass of birds. Nevertheless, there are many fundamental questions that remain unanswered. We will point out some of these questions, in particular those that relate to the quantum nature of the magnetic compass.

## 2. The Radical Pair Mechanism

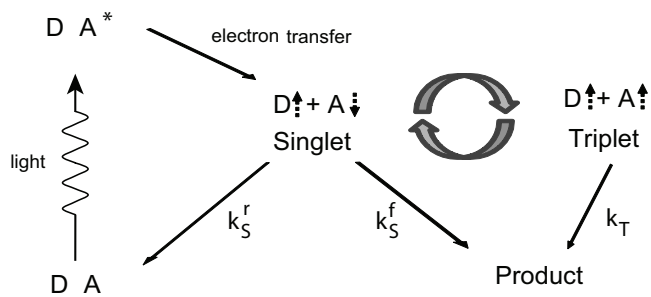


Figure 1: Schematic representation of a possible radical pair reaction scheme sensitive to magnetic field effects. Light activates a donor-pair DA, thereby inducing an electron transfer to create a radical pair, that is, two molecules with an unpaired electron spin each (up and down dotted arrows). Singlet and triplet states, defined by the relative orientation of the electron spins, interconvert due to the combined effects of hyperfine couplings and the external magnetic field. Radical pairs can recombine from the singlet, but not the triplet state. Alternatively, radicals can form a new product state, either from the triplet or singlet state. By affecting the spin states of the radical pair, the external magnetic field regulates the balance between radical pairs recombining and forming product states. The external magnetic field thereby either increases formation of the product state (for enhanced singlet-triplet interconversion) or enhances recombination (for reduced singlet-triplet interconversion) Variations of this reaction scheme are possible; for example, product formation may be spin-forbidden from the singlet state ($k_S^f = 0$), without fundamentally altering the mechanism.

In its simplest form, a radical-pair reaction, following creation of a radical pair e.g. through a light-activated electron transfer, can be described as the combination of two processes, (1) the deterministic interconversion between singlet and triplet states in a spin-coherent radical pair, and (2) the spin-dependent decay of radical pairs into products due to e.g. loss of spin correlation, recombination or separation of radicals in solution. Usually, one simply uses a first-order decay kinetics to describe the fastest of these processes without distinguishing the underlying mechanism.

The combined time evolution of the spins can be described by the stochastic Liouville equation,

$$\dot{\sigma}(t) = -\frac{i}{\hbar}[H, \sigma(t)]_- - \frac{k_s}{2}[P^S, \sigma(t)]_+ - \frac{k_T}{2}[P^T, \sigma(t)]_+ \,. \tag{1}$$

Here, $H$ is the Hamiltonian of the radical pair, $[A, B]_\pm = AB \pm BA$, $P^S$ is the singlet projection operator, $P^T$ is the triplet projection operator, and $k_S$, $k_T$ denote the reaction rates of the decay through singlet channel and triplet channel, respectively. The initial condition for the density matrix is $\sigma(0) = P^S/\mathrm{Tr}[P^S]$, assuming that the radical pair is created in a singlet state,

The fraction $F_S(t)$ of radical pairs in the singlet state at any time $t$ is then

$$F_S(t) = \mathrm{Tr}[P^S \sigma(t)] \,, \tag{2}$$

and the singlet yield $\Phi_S$ is the amount of products decaying via the singlet channel,

$$\Phi_S = \int_0^\infty k_S \, F_S(t) \mathrm{d}t \,. \tag{3}$$

A particularly simple solution to the stochastic Liouville equation (1) exists if the decay rates are spin independent, i.e., for $k_S = k_T \equiv k$. This simplification is justified since the qualitative features of the angular dependence of the yield are primarily determined by the Zeeman interaction between the geomagnetic field and the anisotropic hyperfine interactions; quantitative corrections are necessary for more accurate modeling of the decay kinetics.

For spin-independent decay rates, Equations (2) and (3) reduce to

$$F_S(t) = \frac{1}{N} e^{-kt} \cdot \sum_{m=1}^{4N} \sum_{n=1}^{4N} [P^S_{mn}]^2 \cos[\omega_{mn} t], \tag{4}$$

and

$$\Phi_S = \frac{1}{N} \sum_{m=1}^{4N} \sum_{n=1}^{4N} |P^S_{mn}|^2 \frac{k^2}{k^2 + \omega_{mn}^2} \,. \tag{5}$$

Here, $N$ is the number of nuclear spin configurations and $\omega_{mn} (= \omega_m - \omega_n)$ is the energy difference between eigenstates m and n. As pointed out previously [13, 14, 15], Equations (4) and (5) show that singlet-triplet interconversion is driven by coherent oscillations between eigenstates in the spin Hamiltonian. An external magnetic field results in changes of the eigenstructure of the spin Hamiltonian. If the zero-field Hamiltonian has a sufficient level of symmetry to allow for degenerate eigenstates, the effect of a weak external magnetic field can be understood as lifting some or all of these degeneracies, thereby introducing new channels of oscillations, provided that the respective eigenstates are coupled through coherent links, i.e., off-diagonal elements in the spin Hamiltonian. For a radical pair created in the singlet state, one expects that these oscillations will enhance transitions to the triplet state. A weak magnetic field should therefore decrease the singlet yield in a singlet-born radical pair. An opposite effect occurs due to the Zeeman interaction that shifts the $T^+$ and $T^-$ states away from $T^0$ and, hence, the singlet state for increased magnetic fields, thereby reducing transitions to the triplet state for a singlet born radical. Typically, these two effects of opposite phase occur for different intensities of the external magnetic field. The traditional Zeeman effect can be observed once the Zeeman interaction is stronger than hyperfine couplings mixing the states, i.e. for intensities on the order of 1 mT and above for typical radical pairs. In contrast the so-called *low-field effect* can occur for magnetic fields with intensities weaker than typical hyperfine couplings, i.e. for geomagnetic field intensities. [16, 14, 17, 8].

### *2.1. Spin Hamiltonian*

The general form of the spin Hamiltonian for a radical pair, including hyperfine and Zeeman interactions is:

$$\hat{H} = \hat{H}_1 + \hat{H}_2 \,, \tag{6}$$

where $\hat{H}_1$ and $\hat{H}_2$ denote the Hamiltonians for the two radicals, respectively, defined as

$$\hat{H}_i = \sum_k (a_k^{\,i}\, \hat{S}^{\,i} \cdot \hat{I}_k^{\,i} + \hat{S}^{\,i} \cdot \mathbf{A}_k^i \cdot \hat{I}_k^{\,i}) + \omega_0(\cos\theta \hat{S}_z^{\,i} + \sin\theta\cos\phi \hat{S}_x^{\,i} + \sin\theta\sin\phi \hat{S}_y^{\,i}) \,, \tag{7}$$

where $a_k^{\,i}$ is the $k^{th}$ isotropic hyperfine interaction in the $i^{th}$ radical. $\hat{S}^{\,i}$ is the electron spin operator in $i^{th}$ radical, which is the sum of x, y and z components: $\hat{S}_x^{\,i}$, $\hat{S}_y^{\,i}$ and $\hat{S}_z^{\,i}$, respectively. $\hat{I}_k^i$ is the $k^{th}$ nuclear spin operator in $i^{th}$ radical; $\omega_0$ is the strength of the external magnetic field $B$ converted into frequency units, $\omega_0 = g\mu_B B$. The alignment of the external magnetic field with respect to the radical pair is described by the azimuth and polar angles $\theta$ and $\phi$. $\mathbf{A}_k^i$ is the $k^{th}$ anisotropic hyperfine coupling tensor in the $i^{th}$ radical, in diagonal form,

$$\mathbf{A} = \begin{pmatrix} a_x & 0 & 0 \\ 0 & a_y & 0 \\ 0 & 0 & a_z \end{pmatrix} , \tag{8}$$

where $a_x$, $a_y$ and $a_z$ are the tensor elements along the principal axes of the anisotropic hyperfine interaction with $a_x + a_y + a_z = 0$. One denotes the hyperfine interaction as axially anisotropic if $a_x = a_y$ and as rhombic it $a_x \neq a_y$.

### *2.2. From Magnetic Sensor to Compass*

Magnetic fields will exert effects on the radical pair reaction yield, as described above, even for isotropic hyperfine interactions. However, anisotropic hyperfine interactions are necessary for a radical pair reaction to be sensitive to the direction of the external magnetic field, i.e. to be the basis of a magnetic compass. Theoretically, studies have often employed a single set of parameters to provide a proof of principle that a radical pair can act as a compass [3, 18, 19, 20]. An exception is the systematic study by Timmel and co-workers [15] investigating the most simple possible radical pair, the so-called one proton radical pair with only one spin-1/2 nucleus. Similarly simple models have been useful to explain some of the basic physical principles underlying effects of weak static [14], oscillating [21], and combined static and oscillating magnetic fields [22]. The study [15] demonstrates that low-field effects only occur in radical pairs with axial but not with rhombic anisotropies and predicts a $\cos 2\theta$ dependence of directional magnetic field effects in the limit of long lifetimes and large hyperfine couplings.

A key prerequisite for a physiological magnetic compass is that radical pairs are ordered and anchored in some way lest tumbling or random alignments of radical pairs average out any orientation effects on individual radical pair reactions. This could be most easily achieved if at least one of the radical partners is fixed within a protein environment. The protein itself could then be either embedded in a membrane or anchored to a membrane to restrict directional changes. The question arises how well an ensemble of radical pairs needs to be ordered so as to allow for detection of magnetic field directions. Calculations show that disorder can be significant without necessarily precluding a functioning magnetic compass [23, 24, 25]. The compass function can remain intact provided disorder along one axis is restricted, even if alignments are randomized in the two axes perpendicular. It appears well possible that membrane-associated proteins containing radical pairs can be sufficiently ordered to allow for a functioning compass.

### *2.3. Further Constraints and Open Questions*

For the above described reaction mechanism to operate as a magnetic compass sensor, additional requirements must be fulfilled, as described in [8]. Here we will only point out briefly some of the key chemical requirements. It should be noted that it is experimentally possible to design a radical pair that can satisfy these requirements and can serve as a magnetic compass to earth-strength magnetic fields [5]. Identifying how the functional requirements are fulfilled in a biological environment, remains one of the unanswered questions of the radical pair hypothesis.

**Spin-Correlation Time** The equilibrium argument that magnetic field effects need to be stronger than thermal energies does not apply in the non-equilibrium radical pairs. However, a new requirement needs to be satisfied, i.e. that the rate of spin transitions induced by the external magnetic fields be larger than the rate of processes leading to a loss of spin-correlation. The inverse of this rate, the spin-correlation time, therefore needs to be sufficiently long. A rough estimate of the required spin-correlation time can be obtained by considering that a static magnetic field of intensity B (in $\mu$T) induces an oscillation with a period of about $0.357[\mu s]/B$. Static

magnetic field effects of a 50 $\mu$T field are thus expected to develop for spin-correlation times longer than 700 ns and will level out at about 1 $\mu$s [8]. An upper limit of the spin-correlation time is given by the lifetime of the radical pair which can be on the order of several ms for cryptochromes [26, 27]. Among the longest observed spin-correlation times are those of flavin-based photolyases, closely related to cryptochromes, exceeding tens of $\mu$s [28].

**Spin-Spin Interactions** In addition to the hyperfine and Zeeman interactions that form the basis of the radical pair mechanism, a realistic molecule will have additional interactions between the two electron spins, namely dipolar and exchange interactions. If these interactions are sufficiently large, they can can suppress sensitivity to the external magnetic field. The rationale for neglecting these interactions in simple models is that they decrease for greater distances between the radical partners and that the effects of dipolar and exchange interactions partially cancel for certain distances [29]. Hence, distant radical pairs generated through a cascade of electron-transfer steps might have been evolutionary optimized to achieve distances for which the effects of spin-spin interactions are minimized. A related question is how strong additional intra-molecular interactions, such as strong spin-orbit couplings in one radical affect sensitivity to external magnetic fields. In complex molecules, spin-orbit couplings are quenched, but in molecules with simple symmetries, such as dioxygen or superoxide radicals, spin-orbit couplings dwarf hyperfine coupling strengths.

**Kinetics** In a reaction scheme as the one illustrated in Fig. 1, where a balance between different reaction pathways is achieved, effects of magnetic fields are maximized when the rates for the different competing reactions are equal. Slowing down reaction rates (which can enhance sensitivity to weak magnetic fields) has also to be balanced against concurrent reduction of the quantum yield of radical pair formation. Advantageous regulation of reaction rates in a network of electron transfer reactions may well be a key for enhancing sensitivity to weak magnetic fields and how to do this in a protein environment remains unclear.

## 3. Evidence for a Radical Pair Mechanism

### *3.1. Lack of Evidence for Alternative Mechanisms*

Physical considerations constrain the possible mechanisms by which a 30-60 $\mu$T magnetic field can be detected with biological materials. Next to the radical pair mechanism, discussed here, only two alternative ideas can be considered physically viable, the use of very sensitive electric sensor to detect induction effects and the use of ferromagnetic or super-paramagnetic iron oxide crystals. Electric sensory cells are found in elasmobranch fish, but no similar structures have ever been discovered in land-based animals, including birds. Due to this lack of supporting biological evidence, the induction hypothesis is currently not considered a promising idea. In contrast, an intriguing iron-oxide based system has been found in the beak of birds in the vicinity of endings of the ophthalmic nerve [30]. Moreover, behavioral studies show that the beak system can mediate directional responses with respect to the magnetic field. These responses occur in artificial conditions that differ significantly from the conditions birds encounter on their migratory paths, such as in complete darkness [31] and under certain monochromatic light conditions. These so-called ”fixed-direction” responses differ from ”normal” magnetic compass responses in that there is no seasonal change of direction between the Spring and Fall migratory season, nor an effect of reversing the vertical component of the local magnetic field. Birds become disoriented in conditions leading to fixed-direction responses when their beak is anesthetized, identifying the beak iron oxide system as the likely point for detection of the geomagnetic field. However, under conditions in which birds show normal magnetic compass orientation towards the seasonally appropriate migratory direction, birds' responses remain unaffected by anesthetization [32] of the beak or lesioning of the trigeminal branch or the ophthalmic nerve that connects the beak system with the brain [4]. These results show conclusively that the magnetic compass of birds can operate independent of the beak iron oxide system. It is possible that another, as yet undiscovered, iron-oxide structure exists in birds that underlies the magnetic compass. To test for the involvement of an iron oxide system, one can apply a strong magnetic pulse to re-magnetize or re-organize the magnetic material. If properly applied prior to testing magnetic compass responses, one expects re-oriented or disoriented responses. Such disruptive effects of strong pulses have indeed been observed in some experiments, but when the beak iron oxide system was anesthetized, no effects of strong pulses were observed and birds showed unimpaired magnetic compass orientation [33]. These studies strongly suggest that the primary system responsible for sensing

directional magnetic information is different from the beak iron oxide system, and that it is based on a mechanism not involving iron oxides.

### 3.2. Neurobiology

The radical pair mechanism stipulates that magnetic field effects are perceived as an indirect effect on light sensing. Therefore, the most likely place for the receptors to be located would be in the eye(s) of birds, so as to harness the power and speed of the visual neural processing system. Several immediate questions arise: Are there cells in the eye that host molecules capable of radical pair processes, e.g. cryptochomes? Are there brain centers that are involved in processing magnetic information? Is there a connection between the eye and these brain centers? All of these questions have been answered in the affirmative in the past decade.

Cryptochromes have been identified in the eye of birds [34, 35], in particular in the ganglion cell layer, where they co-localize with cells active during magnetic compass orientation behavior [34]. It is not clear whether these cryptochrome-containing cells are the magnetoreceptors; in fact, the outer segments of photoreceptor cells would be a better location as their inner membranes could provide a scaffold for aligning proteins, a pre-requisite for a magnetic compass, and as they are a more natural point for initiation of a light-dependent signal. Higher resolution studies with antibodies able to enter these cell compartments are still outstanding.

With the means of genetic markers, a brain area termed cluster N has been identified in European robins that is most active during magnetic compass orientation experiments at night [36], when European robins migrate, and much less active during the day or when the eyes are closed [36]. Cluster N is part of the tecto-fugal visual processing pathway and neuronal tracing has shown that it receives input from the eyes through only one synaptic transition [37, 38]. European robins with bilateral cluster N lesions cannot perform magnetic compass orientation [4] but are capable of performing sun and star compass orientation, demonstrating that cluster N is involved in processing magnetic information. It is unclear whether this area is involved in processing compass information in birds like zebra finches, honeyeaters, pigeons and chickens, whose compass operates during daytime and seems to show the same functional properties as the compass of night migrants [39]. This is theoretically possible because there is some activity in Cluster N during the day in zebra finches [36], the only one of these diurnal species in which Cluster N activity has been studied.

*Open Questions*

While neurobiological studies with activation markers lend support to the radical pair hypothesis, so far electrophysiological studies have been unsuccessful in identifying magnetic neurons linked to the visual system whose firing rates are affected by magnetic stimuli. When searching for brain areas processing photoreceptor-based magnetic information in the brain, several caveats are notable. At the level of an individual radical-pair based receptor cell, light stimuli affect the same read-out as magnetic stimuli. It is therefore necessary to separate the effect of a magnetic stimulus from that of a light stimulus. It is not clear what neuronal processing strategies are employed to achieve this separation. However, the employed strategy may have consequences for neurobiological experiments. For example, one possibility for separating magnetic from visual stimuli would be to compare the visual flow speed with the magnetic flow speed when the head of a bird is turned [12]. It is interesting to note that 'head scanning' behavior, i.e. repeated head rotations over more than ±60 degrees, has been observed in some magnetic orientation experiments. Garden warblers corrected their magnetic orientation towards their mean migratory direction immediately after they performed a head scan [40]. If such co-processing of head movements and sensory inputs is used to identify the expected visual flow speed, this may prevent experiments in which the animal's head is fixed. Similarly, experiments, in which the magnetic field is rotated, but the visual input remains fixed, may not allow for processing of magnetic information. Next to the neuronal strategy of separating magnetic from visual stimuli, the point where this separation occurs is also unknown, i.e. it is unclear whether there exists a dedicated magnetic processing channel that transmits magnetic information from the eye or whether visual and magnetic information is co-processed until higher brain areas separate these two types of information.

### 3.3. Cryptochromes - a photo-magnetoreceptor molecule?

Cryptochromes appear to be a particularly intriguing candidate for a photo-magnetoreceptor. They have been found in several of the organisms for which magnetic field effects were demonstrated, including fruit flies, plants and migratory birds and have been shown to act as photoreceptors in a variety of organisms. In plants, they serve

as photosensors for numerous developmental and growth responses such as hypocotyl growth and leaf expansion, induction of flowering time, entrainment of the circadian clock. In animals such as fruit flies, cryptochromes can be involved directly as light inputs into the circadian clock [41].

Most importantly, the photochemical properties of cryptochromes show several features that are favorable for detection of weak magnetic fields (cf. Fig. 2). Firstly, cryptochromes are activated via an intraprotein electron transfer mechanism that generates radical pairs comprising flavin and one of several tryptophan and/or tyrosine residues forming a chain of electron transfer to the surface of the protein [42, 43, 44]. Radical formation in this way activates the protein and induces biological activity. Any physiological or external factor that increases the lifetime of the radical will necessarily result in an increased cryptochrome signal at a given light intensity, and any factor that decreases the lifetime of the radical will result in reduced cryptochrome activity at the same photon fluence (light intensity). Molecular biology and biophysical studies indicate long-lived radical pairs during the photoactivation of cryptochromes [42, 27] and related pigment-protein complexes [26], and recent intriguing results show magnetic field effects on the forward electron transfer reaction in photolyases, which are closely related to cryptochromes [45].

In addition to the forward light dependent (photoreduction) mechanism that activates cryptochromes, they also undergo a reverse reaction (reoxidation) that restores the fully oxidized (inactive resting) form of cryptochromes in the dark (Fig. 2). This reoxidation reaction occurs by a mechanism that could also generate radical pairs (e.g. superoxide and/or peroxide radicals, flavin radicals) and therefore be magnetically sensitive. For example, if applied magnetic fields have an effect on the rate of the reoxidation reaction they would decrease or increase the overall lifetime of the active form of cryptochrome and therefore affect biological activity. In sum, cryptochromes photochemically offers an almost ideal paradigm for magnetosensitivity as even a subtle shift in a redox equilibrium would be perceptible as an alteration in photoreceptor response in the organism.

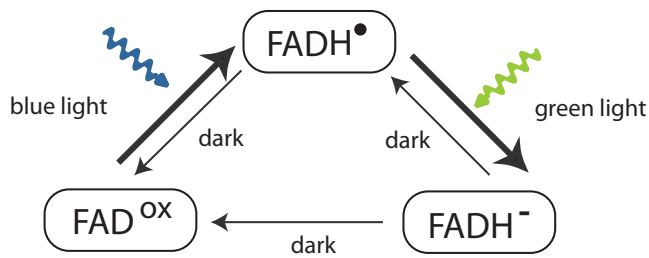


Figure 2: Photocycle of plant cryptochromes. Cryptochromes are bound to a light-absorbing flavin cofactor ($FAD^{ox}$) which can exist in three interconvertable redox forms: ($FAD^{ox}$, FADH, FADH-). In the dark, cryptochrome is found with flavin in the oxidized state ($FAD^{ox}$) which, upon irradiation, undergoes reduction to the FADH form. This reaction requires both electron and proton transfer from nearby amino acid residues in the protein, generating amino acid radicals in turn, which are ultimately reduced through a chain of electron transfer to the protein surface. Further illumination of the flavin radical (by blue or green light) results in formation of the fully reduced FADH- form that is biologically inactive. In the dark, the flavin is spontaneously re-oxidized to restore the fully oxidized resting state through a mechanism that is as yet poorly characterized but involves molecular oxygen and may give rise to superoxide radicals. Therefore both forward and reverse reactions may involve the formation of radical pairs. The degree of cryptochrome activation is governed by the equilibrium reached between the competing forward and reverse reactions under conditions of constant illumination.

Experimental evidence supports such a magnetosensing role for cryptochrome. In the plant system, application of weak magnetic fields to *Arabidopsis thaliana* seedlings indeed causes an enhanced cryptochrome response [46], whereby the plants respond as if they have been exposed to higher intensities of blue light than was in fact the case. The magnetic field effect on hypocotyl growth could not be replicated in a follow-up study, suggesting the presence of as yet unaccounted-for causes of variation [47]. The observed magnetic field effects are consistent with the proposed mechanism of either an increased efficiency in the forward reaction or reduced efficiency of the reverse (dark reversion) reaction of cryptochrome under conditions of applied magnetic field. The physiological responses measured in the exposed plants were inhibition of hypocotyl elongation and anthocyanin accumulation in response to blue light, and their enhanced cryptochrome responsivity was manifested as shortened hypocotyls and increased anthocyanin accumulation as compared to control plants grown under identical light intensities. Although no directional information is conveyed in the plant system, it is a unique example of magnetic field effects in a biological organism mediated by a sensor whose primary purpose is light response. The photochemical reaction mechanism provides an

explanation of how such sensitivity to weak magnetic fields can arise serendipitously in photoreceptors undergoing oxidation/reduction steps during activation.

In the case of fruit fly cryptochromes, a similar effect appears to hold [48]. For the circadian clock, cryptochrome serves to lengthen the period at limiting light intensity, just prior to the onset of arrhythmia. Under conditions of applied magnetic field, the period length of the clock is significantly shortened, indicating enhanced cry signal even though photon fluence (light intensity) is the same. Therefore, application of applied magnetic field in this system mimics the effect of increased blue light signal intensity. Cry mutant or knockout flies showed no magnetic field sensitivity, whereas flies overexpressing cryptochrome showed enhanced sensitivity as compared to wild type. These results provide support for the plant experiments showing that application of magnetic field indeed mimics increased light signal strength from the viewpoint of the photoreceptor. Recent reports investigating the effect of applied magnetic field on a behavioural response of fruit flies, namely the ability to orient towards a food source, has also implicated cryptochrome [49]. In these experiments, flies were trained to associate applied magnetic field with a food source, and learned to use this signal for orientation. The behavioral response also required cryptochrome since it was absent in cry mutant flies. However, although the outcome of these trials involved orientation, the actual physiological effect on the fly is consistent with an intensity sensing effect such as found for plants and for the circadian rhythm effect. Flies could have correlated enhanced (brighter) blue light caused by the applied magnetic field with the food stimulus. As mentioned before, cryptochromes have been found in the eyes of birds [34, 35], and some genetic hints exist for their involvement in magnetoreception [50], but the lack of transgenic birds has precluded more clear-cut evidence so far.

*Open Questions*

The identity of the radical pair that may be responsible for cryptochrome magnetic sensitivity remains unknown. The lifetime of the trp and tyr radicals involved in forward electron transfer is on the order of milliseconds. Although this appears well suited to eventual magnetic sensitivity, recent studies suggests [6, 51] that one of the radicals involved in the bird magnetosensitivity may not be covalently bound to the protein. This could implicate possible additional radicals whose identity remains to be determined. For instance, the nature of the electron donor at the surface of the protein is unknown and there may be a relatively long lived radical formed at the terminal step where the surface tryptophan or tyrosine is reduced by solvent. Furthermore, it is possible that there may formation of radicals during the dark reversion reaction involving e.g. oxygen or superoxide radicals [6, 51]. These pathways need to be additionally explored.

Theoretically, modeling needs to proceed from proof-of-principle models to more realistic models including structural, physical, and chemical details. Genetic studies show absence of magnetic field effects when cryptochromes are deleted, but one yet needs to show that introducing cryptochromes into a system creates magnetic sensitivity, ideally with a hint of the evolutionary advantage of such sensitivity. The small size of magnetic field effects suggest that we yet have to find physiological responses for which the magnetic field provide the dominant, and not incidentary stimuli.

### *3.4. Radio Frequency Effects on Magnetic Orientation*

As discussed above, one can investigate a possible involvement of an iron-oxide based compass by observing a disruptive effect of a strong magnetic pulse, applied prior to a magnetic orientation experiment. Oscillating magnetic fields with a frequency that matches the energetic splitting between singlet and triplet states are expected to affect singlet-triplet interconversion and thereby destroy or change the sensitivity of a radical pair to the geomagnetic field. Since the chemical nature of the hypothetical radical pair in birds is unknown, one cannot predict exact frequencies *a priori*. However, typical hyperfine couplings and the Larmor frequency of the geomagnetic field suggest that fields with frequencies on the order of 1-100 MHz should disrupt or change magnetic orientation responses. Thus, such oscillating fields can serve as a diagnostic tool in orientation experiments for the radical pair mechanism, analogous to the strong pulses for iron-oxide based mechanisms.

Fig. 3 summarizes the results of applying oscillating magnetic fields in magnetic orientation experiments with European Robins. Fig. 3 presents a compilation of results obtained between 2004 and 2007 that are presented in more detail in Figs. 5 and 6 in [1]. In all conditions, the oscillating magnetic field was applied in addition to the static magnetic field of either 46 $\mu$T (geomagnetic field) or an amplified static field of doubled intensity. The static field was aligned at a 66° angle with the horizon, whereas the linear polarized oscillating field was applied vertically, thus forming a 24° angle with the static magnetic field. At an intensity of about 1% of the geomagnetic field, linear

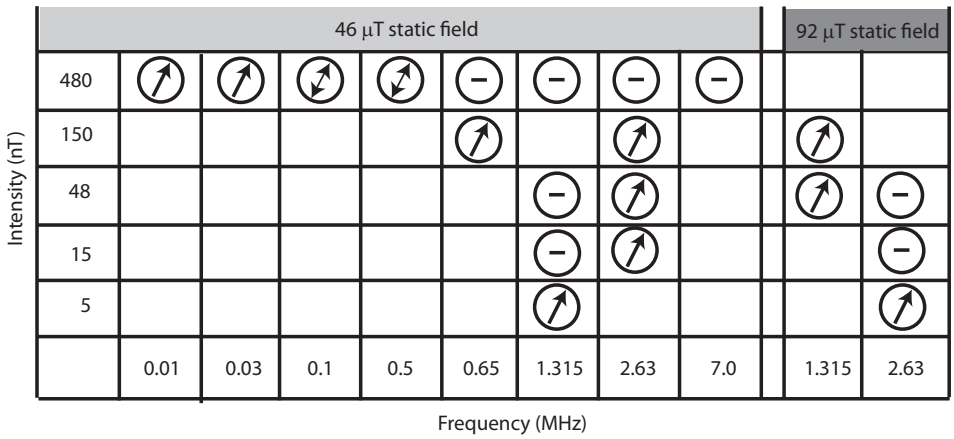


Figure 3: Effects of oscillating magnetic fields on magnetic orientation of European Robins. European robins responses were recorded in funnel-shaped cages illuminated by diffuse light from above. In addition to the local magnetic field, an oscillating magnetic field of the indicated intensity and frequency was applied in each experimental condition. For details see [52, 6]. The outcome of the experiments is presented as follows: Circles with minus signs denote disorientation, circles with a single upward arrow denote statistically significant orientation in the appropriate migratory direction and circles with a double-headed arrow denote axial responses.

polarized oscillating fields disrupt orientation of European Robins for frequencies between 0.65 and 7 MHz. Higher frequencies were not tested due to limitations of the coil design. At frequencies below 30 kHz, oscillating fields did not affect orientation of Robins, and at 0.1 and 0.5 MHz, birds showed bimodal orientation, suggesting a transition region between oriented and disoriented behavior. These results have been interpreted as suggesting a spin-correlation time of 2-10 $\mu$s [6]. Clearly, an oscillation field with a period longer than the spin-correlation time would be effectively static and addition of a weak static magnetic field of 1% of the geomagnetic intensity is not expected to have an effect.

There is a much more pronounced disruptive effect of oscillating fields at 1.315 MHz, corresponding to the free electron Larmor frequency in the geomagnetic field of 46 $\mu$T. At this frequency, a 15 nT field led to disoriented behavior, whereas about 30 times stronger fields were necessary to disorient birds at other frequencies. These observations suggest that one of the electron spins is a free electron spin, i.e. that it is located in a radical with no hyperfine or other other interactions. This suggestion is bolstered by the two further observations. When the static field intensity is doubled, the frequency at which a 15 nT field leads to disorientation is also doubled, as one expects for a Zeeman resonance at the free electron Larmor frequency. In the absence of internal magnetic fields, the geomagnetic field provides the strongest magnetic interaction at the point of the free electron spin and therefore the same selection rules apply as for electron spin resonance effects in much stronger static fields. In particular, effects of the oscillating fields are only expected to occur if the oscillating field has a component perpendicular to the static field. When the oscillating field was applied parallel to the geomagnetic field, birds showed orientation in the expected migratory direction that was indistinguishable from control [52, 53], consistent with a radical devoid of hyperfine interactions. A particularly strong disruptive effect of oscillating magnetic fields at the free electron Larmor frequency has been observed in all species for which effects of oscillating fields on magnetic compass orientation have been found, namely in migratory European robins, the non-migratory chickens [39] and Zebra finches [54] as well as in cockroaches [55]. This suggests a similar chemical nature of the magnetically sensitive radical pair reaction across different species. Radicals with a free electron spin are unusual in organic environments, as they need to be devoid of hydrogen or nitrogen atoms. The chemical nature of this postulated radical remains unknown. Superoxide and dioxygen radicals have been suggested as possible candidates [6, 51], but cannot be reconciled with the observed spectral properties [56].

As with any disruptive effect, it is necessary to address the question whether the change in orientation is due to a direct effect on the magnetic compass or whether it is due to an unrelated non-specific effect, e.g. a change in motivation due to the presence of the oscillating fields. Oscillating fields had no effect on the magnetic compass of mole rats, a blind, sub-terranean animal whose compass is likely based on iron oxide materials [57], indicating that oscillating fields appear to be specific to the radical pair mechanism. The geomagnetic field in Frankfurt, where the experiments were conducted, forms a 66° angle with the horizon. A key control observation is that the angle of

the oscillating fields with the geomagnetic field is a determining factor for whether birds are oriented or disoriented [52, 53]. Birds were disoriented when the oscillating fields formed a 48° (or 24°) angle with the geomagnetic field, but not when they were collinear with the geomagnetic field. The choice of 48° is particularly meaningful as a control condition, because at this angle, the oscillating field is applied at the same angle relative to the horizontal plane, in which the birds move during the experiments, as in the 0° condition, as illustrated in Fig. 4 in [1]. There is no reason why the birds' motivation should be affected differently by non-specific effects of oscillating fields of equal intensity, frequency, and angle with respect to the birds, but birds orient in one condition (0°) and not the other (48°). It appears much more likely that oscillating fields affect the mechanism by which birds detect the direction of the geomagnetic field. As discussed above, the absence of oscillating magnetic field effects is expected if one radical is devoid of hyperfine interactions.

Given that earth-strength magnetic field effects have only been observed in one specially designed radical pair reaction so far, but not in the vast number of radical pair reactions studied in spin chemistry, it appears extremely unlikely that several of the naturally occurring radical pair reactions in birds happen to be sensitive to earth-strength magnetic fields. Rather, one would expect that evolution led to selection of an unusually sensitive radical pair reaction for the purpose of detecting and using magnetic information. Nevertheless, one might consider the unlikely possibility that the observed effects of the oscillating magnetic fields are due to effects on a radical pair reaction sensitive to the direction of the geomagnetic field that is not part of the magnetic compass, but of an unrelated biochemical pathway that somehow affects orientation responses. However, effects of oscillating fields were observed only on normal magnetic compass orientation responses and not on fixed direction magnetic responses of birds, lending further support to the assertion that the affected radical pair is indeed part of the magnetic compass. It would be desirable to test effects of oscillating fields also on sun or star compass orientation responses since the biological significance of the fixed-direction responses remains unclear.

*Open Questions*

**Interpretation** The conceptual similarity of the behavioral experiments with oscillating magnetic fields and of electron spin resonance measurements is well documented, but has perhaps been over-emphasized in initial presentations. One obvious and important difference between the two kind of measurements is that electron spin measurements detect the effects of the oscillating fields directly at the spin states of the radical pair, whereas the behavioral experiments detect their effects indirectly via their influence on orientation decisions. Presumably, the effects at the radical pair spin states are converted via an unknown signal transduction mechanism into concentration changes of a signaling molecule, possibly through a cascade of amplification steps, before these concentration changes are converted into nerve impulses that are then interpreted in a yet unknown way for a bird to reach an orientation decision. It would be very naive to assume that changes on the spin states lead to quantitatively similar effects on orientation decisions and even qualitatively different effects cannot be excluded.

**Spin Correlation Time** The intensity of the oscillating field at 1.315 MHz required to disrupt orientation is remarkably weak, less than 0.3 per thousand of the geomagnetic field intensity. At such weak intensities, the rate of spin flips is very low, requiring very long spin-correlation times of the radical pair for oscillating magnetic field effects to become detectable. A rough first estimate of the required spin-correlation time can be obtained by considering that the periodic interconversion induced by a 50 nT and a 15 nT Zeeman interaction has a period of about 700 $\mu$s and 2 ms, respectively. There is no reason to assume that effects of oscillating fields require longer spin-correlation times than effects of static fields.

One can numerically evaluate the effect of oscillating magnetic fields on the yield of radical pair reactions. Fig. 4 shows the effect of adding a 50 nT static or oscillating field on top of a 46 $\mu$T static field on the reaction yield of a simple radical pair with only one spin-1/2 hyperfine interaction of 3.93 G. The additional field was added at a 24° angle to the 46 $\mu$T static field, as in the experimental situation. For spin-correlation times above several $\mu$s, the effects of a $\approx$46 $\mu$T static magnetic field on the radical pair reaction yields have reached saturation. Changing the intensity of the static field by another 50 nT produces a very small change in the reaction yield (about $10^{-5}$) and this change does not increase for longer lifetimes of the radical pair. In contrast, a resonant oscillating magnetic field at the Larmor frequency, i.e. 1.315 MHz for a 48$\mu$T field produces a change in the reaction yield that increases with longer lifetimes and only levels off for lifetimes in excess of several ms. These calculations show that even minute oscillating magnetic fields can produce sizeable changes in radical

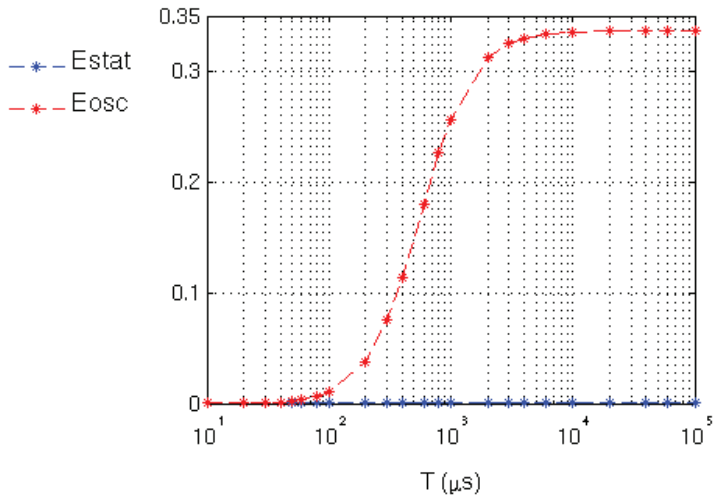


Figure 4: Size of on-resonance effects of a 50 nT oscillating magnetic field added to the geomagnetic field at the free electron Larmor frequency. The graph shows the change in singlet yield due to the oscillating field for a radical pair with one isotropic hyperfine interactions and various spin-correlation times $T = 1/k$. Sizeable effects occur for spin-correlation times exceeding 100 $\mu$s. In comparison, addition of a 50 nT static magnetic field has only a minute effect on the yield (about $10^{-5}$) that does not increase with longer lifetimes.

pair reaction yields for radical pairs with spin-correlation times exceeding 100 $\mu$s. While these calculations were performed for a particularly simple radical pair, it is reasonable to expect qualitatively similar changes for more complex radical pairs provided that one radical remains devoid of hyperfine couplings. Based on these calculations, we do not agree with the estimate put forward based on perturbation theory approaches that a spin-correlation time upwards of 1 s is a prerequisite for effects of weak (<100 nT) oscillating magnetic field to occur [58]. However, the estimates put forward here make it easier to explain the experimentally observed oscillating magnetic field effects for spin correlation times exceeding 100 $\mu$s. At 10 $\mu$s, the effect of a 50 nT oscillating field at the Larmor frequency is about a 0.1 % change of the radical pair reaction yield. While it is not impossible that such small changes lead to disorientation, changes on the same order as the effect of the geomagnetic field on reaction yields would be a much more obvious cause for disorientation.

We are therefore left with two possible estimates of the spin-correlation time. The estimate of 2-10 $\mu$s, mentioned above, is based on interpreting the transition between oriented and disoriented behavior as caused by the transition from oscillating to effectively static fields. The challenge for this interpretation is the small size of on-resonance magnetic field effects of a 15 nT magnetic field, that are less than 0.1 % of the yield. While it is not impossible that such small changes lead to disruption, the possible mechanism causing disorientation remains unclear. On the other hand, an estimate of a > 100 $\mu$s spin correlation time leads to much larger on-resonance effects, but does not offer an immediate answer as to why a transition between oriented and disoriented behavior occurs between 2-10 $\mu$s. Calculations are necessary to see whether the onset of resonances with splittings induced by hyperfine couplings might explain this transition. Moreover, a 100 $\mu$s spin-correlation time is also longer than spin-correlation times observed in organic molecules so far. Transient absorption measurements show that radical pairs in garden warbler cryptochromes persist for tens of ms, but do not provide information about the spin-correlation time of these radical pairs [26].

**Mechanism of Disruption** It is very difficult to address is the question by which precise mechanism oscillating magnetic fields disrupt orientation. At the radical pair, oscillating fields change the amplitude of the isotropic reaction yield, but also the form and amplitude of the reaction yield anisotropy and, hence, of the signal modulation patterns formed due to the magnetic field [8]. While it is intuitive that larger changes of these observables are more likely to produce a disruptive effect, there is no a priori way to tell whether a 10%, 1%, 0.1% or any other level of change is sufficient to disrupt orientation. One first needs to determine the signal transduction

mechanism and in particular the signal-to-noise ratio of a radical-pair based magnetic compass. The oscillating field can then be treated as an additional, artificial source of noise. If the magnetic compass is fairly fragile, i.e. its signal-to-noise ratio is low, and the signal transduction mechanism involves strong amplification steps, then even surprisingly low levels of oscillating field noise might be sufficient for disrupting the measurement. At present, we lack virtually all molecular details necessary to evaluate the efficiency of the magnetic signal transduction mechanism in a similarly quantitative fashion as has been done for visual signal transduction [59]. For example, it is not even clear whether a magnetic signal is initiated in a single cell or whether it involves a multi-cellular signal transduction mechanism [60].

One possibility for the mechanism of disruption that has been discussed is that the oscillating magnetic field might change the operating point of the radical pair system outside of a functional window. It is an intriguing feature of the magnetic compass of birds that it possesses a functional window: A change of the static magnetic field intensity by about 25% upwards or downwards leads to disorientation. However, this effect is temporary. After birds are exposed to the new intensity for a certain amount of time that can be as short as 1h [61], they show oriented responses in the new intensity. Testing birds after pre-exposure to oscillating fields can inform whether the effect of the oscillating field is comparable to or different than the shift of the functional window observed for static field intensity changes.

**Quantum Control of Birds** The successful application of artificial oscillating magnetic fields to disrupt orientation behavior in a reproducible fashion raises the question whether one might use artificial fields *instead of* the geomagnetic field to inform directed responses of birds. This is a considerably more challenging task; for a disruptive effect, the radical pair spin states only needs to be altered in some way that makes it harder for birds to interpret magnetic information. In contrast, to enable oriented responses, one needs to find artificial magnetic fields that nearly exactly reproduce the effect of the static magnetic field on the spin states of the unknown radical pair.

One way this might be achieved is by applying only oscillating magnetic fields. Such fields are theoretically expected to affect radical pair spin states and, hence, reaction yields in a similar fashion as static magnetic fields, provided that their intensity is in the same order of magnitude.

From a theoretical perspective, the description of a spin system in a radical pair can be translated seamlessly into a quantum control description. There is growing interest in the question whether quantum mechanics plays a non-trivial role in the magnetic compass of birds [62**?** ], for example whether entanglement would theoretically enhance magnetic sensitivity of birds or, even if not [62], if entanglement is realized in the bird's spin system. What appears an esoteric question at first sight can pave the way to new approaches. A recent study suggests that quantum control pulses could also be a means to allow a bird to obtain directional information [62]. Should one be able to orient an animal with the use of quantum control pulses, this would not only make it much harder to explain the results without recourse to a radical pair mechanism, but might also allow measurement of coherence times by variation of the pulse length. The theoretically required power density of GW/m$^2$ all but precludes the application of quantum control pulses in the rather sizeable bird testing cages, but one might be able to realize such measurements for other animals, such as fruit flies that use smaller test arenas or in measurements with cryptochrome protein.

## 4. Conclusions

The last decade has seen a considerable number of studies from different fields supporting the photo-magnetorecepto and cryptochrome hypotheses. However, as described here, fundamental questions remain in all relevant fields. Biophysically, we yet have to understand how nature designed radical pair receptors so that they can be sensitive to earth-strength magnetic fields at physiological temperatures, a feat that has been approximated, but not yet fully accomplished in man-made radical pair reactions. Behavioral experiments with radio-frequency fields strongly support the existence of a radical-pair mechanism in birds, but provide so far limited insight into the chemical nature of the radical pair involved. Studies at the protein level suggest that cryptochromes have properties conducive for magnetic sensing, such as formation of long-lived radical pairs. But, earth-strength magnetic field effects have yet to be seen on cryptochromes or any other concrete candidate photo-magnetoreceptor, both at the protein level, and in vivo. Genetic

studies show absence of (larger than earth-strength) magnetic field effects in some organisms when cryptochromes are deleted, but true model organisms for genetic studies of photoreceptor-based magnetoreception are still lacking. In such a model, one should then show that introducing cryptochromes or regulating the expression levels can create magnetic sensitivity, ideally with a hint of the evolutionary advantage of such sensitivity. A brain area has been identified that is necessary for magnetic orientation behavior, but the processes underlying magnetic processes remain unknown and neurons responsive to magnetic stimuli have yet to be identified. The new, tentative link to quantum information approaches may be helpful in suggesting new approaches. Certainly, if birds can be shown conclusively to use a radical-pair based compass, this would be a dramatic example of the use of a coherent quantum-mechanical process in biology.

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