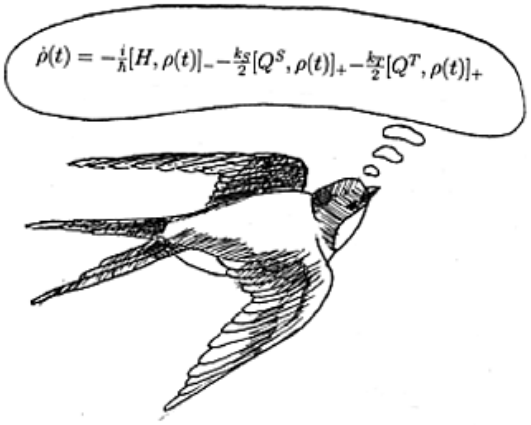
Animal magnetoreception

Radical pair based molecular compass hypothesis



Introduction

Behaviour studies showed that many animals can sense the magnetic field of the Earth and use this information for navigation. For example sea turtles, sharks, rays, newts, fruitflies, and various species of birds: pigeons, European robins, garden warblers. These ethological assays make us know some important properties of this sensing process, but the underlying sensing mechanism(s) and the information projecting and processing neural pathways are still pretty unknowns. Makes the research field hard but interesting that we, humans do not sense the surrounding magnetic field consciously, so we cannot search ourselves and cannot really imagine, how this information represented in the brain, what kinds of feelings it produces. In facts, it took a long time to realise; this sense exists in various creatures. The research nowadays has two main parts: studying animal behaviour in specific conditions, and making theoretical models satisfying the observations. Verifying the behaviour observations is difficult, because the complexity of the nervous system and the conditions, we cannot really know, is there a change in the sensing (we do not know, where it is and how it looks like) or the behaviour occur because of the motivation: the lab conditions are far from the naturals, and in the nature there are a lot of uncontrollable noise factor. In models we often do not know exact chemical structure for the candidates of the processes, and/or we do not have the calculation tools for the complexity of real organic molecules and the conditions of a living system. Below, I will list the leading theories of the field and write a bit more detailed about one of them, the photochemical reactions.

There are three main hypotheses about the sensing mechanic field. We can distinguish them based on if they are sensitive to polarity of the magnetic field or just sense the inclination. They have different sensitivity and can be disrupted with different effects. There are observations and theoretical models for all the alternatives, but none of them are exactly proofed yet, we only know they could be solutions for magnetoreception in some partly unknown conditions.

One of is the electromagnetic induction model. This is mainly mentioned in connection animals living in sea water, sharks and rays. According to this hypothesis, jelly-filled canals on the fish, known as ampullae of Lorenzini, function as the conducting bars; the surrounding sea water functions as the motionless conducting medium and the highly resistive and sensitive electro receptors at the inner end of the ampullae detect the voltage drop of the induced current. One of the problems is there are lot's of inner and outer conditions that generate induction, so there are significant noise to filter in order to find the information comes from the Earth magnetic field. It could be a polarity compass, but probably not sensitive enough to be used as a geomagnetic mapping mechanism. (1.)

The second is the biogenic magnetite hypothesis. It is based on the discovery of magnetic minerals (i.e. Fe_3O_4) in organisms, for example bacteria, trout and pigeons. These creatures react to the magnetic field: colony growing patterns in bacteria depend on the external field, and changing the magnetic conditions cause the disorientation of salmons, pigeons. If the particles are bigger than 50 nm, we talk about single-domain crystals, if smaller, super-paramagnetic crystals. That has different properties. Unlike single-domain crystals, they do not have a permanent magnetic moment and so cannot physically rotate into alignment with the Earth's field. Instead, the magnetic axis of a super paramagnetic crystal tracks the axis of any ambient field, even though the crystal itself remains stationary. Single-domain crystals were found in the found mainly in fish, and the super-paramagnetic ones in the upper beak of birds. These are in the membrane of the nerve terminals and likely to influence the opening of potassium channels based on the actual strength and orientation of the magnetic field. The magnetite crystals are the most sensitive for the soft changes of the Earth-strength magnetic fields, so they can be used for mapping an area in this way, not only for a compass (single-domains could detect polarity, super-paramagnets only the inclination). For neural connections: electrophysiological recordings showed, magnetic stimuli have an effect on the ros branch of the trigeminal (V.) nerve in fish and on the trigeminal ganglion (through the ophthalamic branch) in pigeon. (1.)

Radical Pair Reactions:

This essay is mainly written about this third theory of magnetoreception, the influence of Earth-strength magnetic fields on chemical reactions. This process is intensively searched in connection with the newts, fruitfly and avian for example European robin, silvereye and garden warblers. Behaviour studies (the European robin is the best known species by the intensive research in Wolfgang Wiltschko's lab) showed, that the robin can only orient in shorter wavelength blue (443nm) and green (565nm) light, but not in red. Another important facility of this sensing, that it is inclination based: sense only the orientation of the field vector but not the polarity. The polarity maybe comes from the comparison of the implication vector and the gravity vector (4.). These properties and the sensitivity of radio frequency impulses are the clues that oriented the researchers to the radial pair reactions as a promising mechanism to answer the question of migrating navigation of these birds.

A radical pair, most generally, is a pair of molecules, each of which has an unpaired electron. If the radical pair is formed so that the spins on the two unpaired electrons in the system are correlated (i.e. they begin in a singlet or triplet state), and the reaction products are spin-dependent (i.e., there are distinct products for the cases where the radical pair system is in an overall singlet vs. triplet state), then there is an opportunity for an external magnetic field to affect the reaction by modulating the

relative orientation of the electron spins. (5.) (Fig. 1. (3.)) The singlet state is when the spins of the electrons are antiparallel (↑↓), the triplet is when the spins are the parallel (↓↓ or ↑↑). Spin correlation happens often by a sequential electron transfer starts with absorbing a photon.

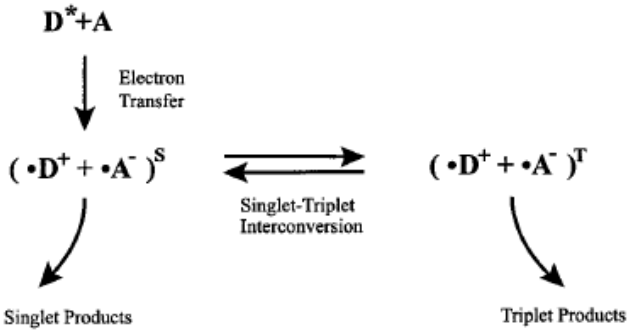


FIGURE 1 Reaction scheme for a radical pair reaction with magnetic field-dependent reaction products. The radical pair is generated by an electron transfer from a donor molecule *D* to an acceptor molecule *A*. An external magnetic field affects interconversion between singlet and triplet states of the radical pair.

An absolute requirement is that between the 2 radicals, have at least 1 hyperfine interaction, i.e., an intraradical coupling between the magnetic moment of the unpaired electron and the magnetic moment of an atomic nucleus such as ^{1}H or ^{14}N. Almost all biologically occurring radicals have several potentially suitable hyperfine interactions.

Hyperfine interactions are crucial because they drive the interconversion of the S and T states of the radical pair and allow it to be modified by an external magnetic field. S↔T interconversion is a coherent quantum mechanical process: Radical pairs oscillate between their S and T states at a variety of frequencies determined by the strengths of the hyperfine interactions. ^{1}H and ^{14}N hyperfine couplings in organic radicals are typically in the range 10–1,000 μT, corresponding to frequencies of 300 kHz to 30 MHz (the conversion factor is 28 kHz μT^{-1}). The time scale for significant transformation of S into T and vice versa is thus typically 10 ns^{-1} μs. Sensitivity to an external magnetic field arises because the Zeeman interaction of the magnetic moments of the 2 electrons causes additional periodic S↔T interconversion. In a 50μT field, this oscillation has a frequency of about 1.4 MHz and a period of about 700 ns. The calculated time dependence for a prototype radical pair is shown in Fig. 2. (2.)

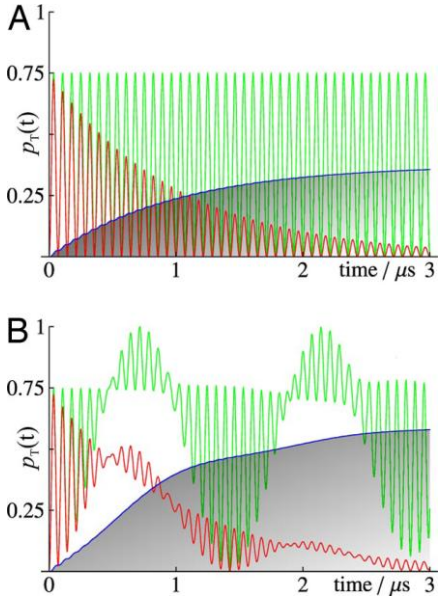


Fig. 2. Quantum mechanical spin dynamics simulations: (A) In the absence of the magnetic field and with no recombination (green), the fraction of radical pairs that exist in the triplet state, pT(t), oscillates at the frequency of the hyperfine coupling (here 14 MHz). (B) When a weak magnetic field is introduced (green), pT(t) shows an additional, slower, modulation at the frequency of the Zeeman interaction (here 1.4 MHz). The radical pair reactions cause pT(t) to be exponentially damped (red) and allow the reaction product to accumulate (blue). The applied magnetic field (50 μT) results in an increased transient conversion of the radical pair into the triplet state, causing the triplet product to be formed more rapidly and in higher yield. Faster recombination than shown here would allow scant time for the slow modulation arising from the Zeeman interaction to alter pT(t); the yield of triplet product would then be much less affected by the field. (2.)

The magnetic field of the Earth is about 50μT(=0,5G), it is more than 6 orders of magnitude smaller than the average thermal energy *k*B*T*, which in turn is 10–100 times smaller than the strength of a chemical bond. (2.) So this weak magnetic field can modify theoretically the product yields of a chemical reaction by the hyperfine coupling effect. But it needs a special time window, because if the radical pair has too long life time the spins get separated and if too short, the difference in yields cannot be detected. In the reference no. 2 there are more constraints for the appropriate radical pair: geometry, disorder, motion, reaction kinetics. And for function as a compass the answer for the magnetic field must be anisotropic, must depend on the relative position of the molecule and the magnetic field vector.
An other observation that is consistent with the radical pair mechanism is that (unlike magnetite) it can be disturbed by low strength radio waves of approximately the same energy as that of the interaction between the spin states and the Earth's magnetic field. Broadband radio noise (0.1–10.0 MHz) and a constant frequency signal of 7 MHz both disrupted magnetic orientation in European robins. (For details, see the research of Thorsten Ritz's and Wolfgang Wiltschko's lab.)

Building models, which satisfy all the criteria, is a hard task, but not impossible (see ref. 3. and 7. for details). For example the Hamiltonian of a radical pair is look like this:

$$H = \sum_{k=1,2} H_k = -\gamma_e \vec{B} \cdot \sum_k \vec{S}_k + \sum_{k,j} \vec{S}_k \cdot \hat{\lambda}_{k_j} \cdot \vec{I}_{k_j}$$

where $\gamma_e = -g_e \mu_B$ is the electron gyromagnetic ratio, $\hat{\lambda}_{k_j}$ denote the hyperfine coupling tensors and $\vec{S}_k$, $\vec{I}_{k_j}$ are the electron and nuclear spin operators respectively. (7.)

And the singlet yield can be calculated in this way:

$$\Phi_s(t) = \int_0^t r_c(t) f(t) dt$$

where $r_c(t)$ is the radical re-encounter probability distribution, and $f(t) = \langle \mathbb{S} | \rho_s(t) | \mathbb{S} \rangle$ is the fidelity between the electron spin state $\rho_s(t)$ at time t and the singlet state. (7.)

For the model the stochastic Liouville equation also needs (3.), which is shown above on the 1. picture after the title.

After these the question arises, could we implement this theoretical possibility, are there or can we build molecules, work as an implication compass? The answer is yes, because in 2008 was published, that Green-light irradiation of a carotenoid, porphyrin, and fullerene triad molecule produced a radical pair whose lifetime was both sensitive to magnetic fields less than50 μT and that responded anisotropically. Frozen solutions at low temperatures were used in these experiments to immobilize the molecules, which were either aligned in a liquid crystalline solvent or probed anisotropically using photoselection with plane-polarized light. Although this triad is not ideal as a compass, [$C^{\cdot+}$–P–$F^{\cdot-}$] does have several favourable properties—it is rapidly and efficiently formed by absorption of light and is long enough lived to allow an about 50 μT magnetic field to have a detectable effect on its spin dynamics. Furthermore, the radical centres are sufficiently separated (which minimizes interference

from radical–radical exchange and dipolar interactions), whereas their fixed relative orientations and restricted molecular motion in frozen solution result in minimal static and dynamic averaging of the crucial anisotropic magnetic interactions. A further attractive feature of [$C^{\cdot+}$–P–$F^{\cdot-}$] is its highly unsymmetrical distribution of magnetic nuclei, a feature associated with optimum isotropic and anisotropic magnetic field effects. However, both its recombination and spin relaxation, jointly responsible for the biphasic time dependence, are fast enough (even at 113 K) to attenuate the, 50μT signal. Responses closer to the theoretical maximum of 20–40%, expected for spin correlation lifetimes>1 μs would have allowed the anisotropy measurements to be performed at much lower fields than, 3 mT. (Fig. 3.)(6.)

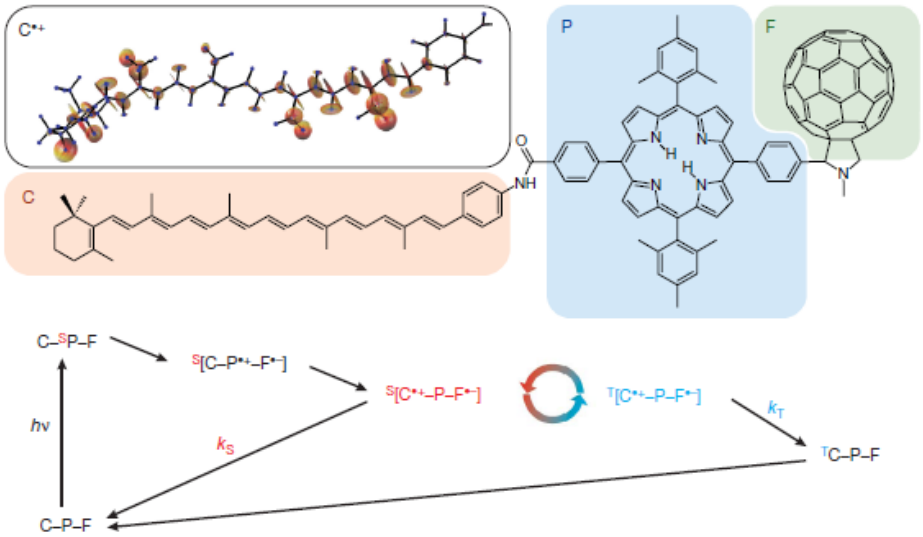


Fig. 3. **C–P–F triad.** Structure (top) and reaction scheme (bottom) of the C–P–F triad used to demonstrate the principle of a chemical compass. The interconversion of the singlet (S) and triplet (T) states of the radical pair [$C^{\bullet+}$–P–$F^{\bullet-}$] is driven by magnetic hyperfine interactions and is modulated by the Zeeman interaction with an external magnetic field. [$C^{\bullet+}$–P–$F^{\bullet-}$] can recombine spin-selectively, with rate constants k_S and k_T. As the hyperfine interactions are anisotropic, and $k_S \neq k_T$, the lifetime of the radical pair reaction depends on its orientation with respect to the external magnetic field. The inset at top left is a representation of the anisotropic hyperfine interactions in $C^{\bullet+}$; 22 of the 46 protons in this radical have isotropic hyperfine couplings larger than 100 μT. $F^{\bullet-}$, by contrast, is almost devoid of hyperfine couplings. *hν*: light excitation.

The Cryptochrome hypothesis:

After these, the question arises, can find a molecule with the required properties in the animal's body and does this molecule cause magnetoreception? A good candidate has to be connected with the nervous system in order to give an input to sense, and it need to be positioned in a way to get photons to absorb. So it should be in the eye of the bird (for newts the pineal gland also an applicant). Behaviour studies confirm that, blind birds cannot sense the magnetic field. Nowadays based on behaviour, genetical experiments and theoretical calculation models the most promising candidates are the protein cryptochromes for functioning as a molecular compass.

Cryptochromes are 50- to 70-kDa blue-light photoreceptor flavoproteins, first identified in plants in 1993 and since found in bacteria, insects, and animals. They contain 2 noncovalently bound chromophores: a redoxactive flavin adenine dinucleotide (FAD) and a light-harvesting cofactor.

Their functions, not all of which require light activation, include entrainment of circadian clocks and, in plants, regulation of growth and development. Unlike their evolutionary ancestors, the DNA photolyases, to which they show high sequence homology and structural similarity, cryptochromes do not repair double-stranded DNA. (2.)

Detailed analysis of cryptochrome as a transducer for the avian compass would require an atomic-resolution structure of the protein, and unfortunately, no structure of avian cryptochrome is currently available. However, the structure of cryptochrome from a plant (Arabidopsis thaliana) is available, and the cryptochromes of plants and birds are structurally very similar. (5.) (Recent experiments showed that magnetic intensity affects cryptochrome-dependent responses in Arabidopsis thaliana: seedlings exhibit a magnetic field effect. Processes involved with cryptochrome signalling are enhanced under a magnetic field of 5 G, 10 times bigger than the Earth's magnetic field. This fits with the avian compass models. And genetics also showed that fruitfly mutants with cryptochrome absence cannot orient in the magnetic field.) So we have some evidence that this could be the compass molecule, but the calculations by now were only taken with Arabidopsis cryptochrome or with photolypase.

There are two possibilities for magnetic field based radical pair reaction in cryptochrome can act as a compass, one of them is the activation of FAD to $FADH^{\cdot}$ by three tryptophan, the other is the superoxide based back reaction. The reference number 5 is a very useful summery of both mechanisms, so I will use this below to describe them.

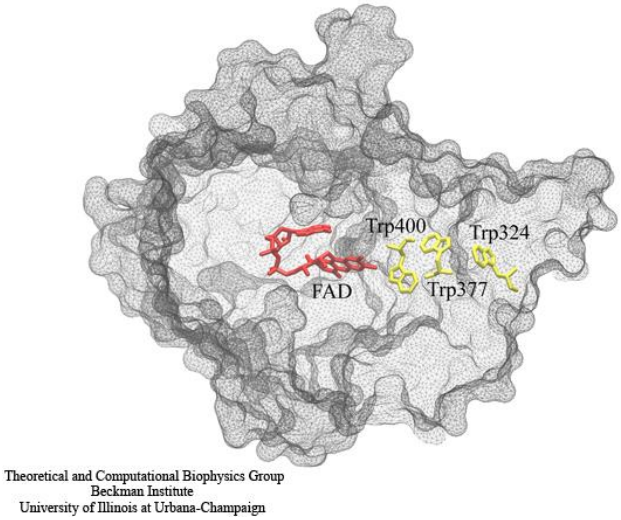


Fig. 4. A chain of three tryptophan residues, Trp400, Trp377 and Trp324 are involved in the photoreduction of the FAD cofactor. During the electron-transfer process, radical pairs are formed between FADH and each of the tryptophans. The formation of these radical pairs permits a magnetic field effect in cryptochrome.

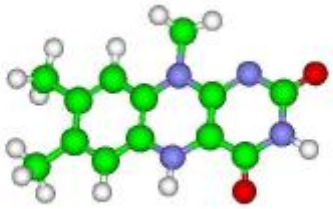
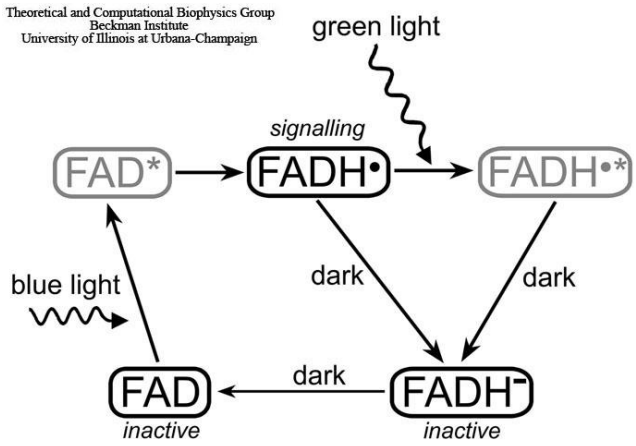


Fig. 5. Here is the molecular structure of the flavin radical FADH•. Green: Carbon; Grey: Hydrogen; Blue: Nitrogen; Red: Oxygen.
We consider the dominant hyperfine couplings from two spin-1 nitrogen nuclei and three spin- 1 hydrogen nuclei. (7.)

The activation reaction:

Both photolyase and cryptochrome internally bind the chromophore flavin adenine dinucleotide (FAD). In photolyase, the protein is brought to its active state via a light-induced photoreduction pathway involving a chain of three tryptophans. Studies suggest that cryptochrome also is activated by a similar photoreduction pathway. The hypothesized photoreduction pathway in cryptochrome involves three tryptophans conserved from photolyase, numbered Trp324, Trp377 and Trp400 in the *Arabidopsis* cryptochrome structure. Trp324 is located near the periphery of the protein body, and Trp400 is proximal to the flavin cofactor with Trp377 located in between. Before light activation of cryptochrome, the flavin cofactor is present in its fully oxidized FAD state. FAD absorbs blue light photons, being promoted thereby to an excited state, FAD^{*}. FAD^{*} is then protonated, likely from a

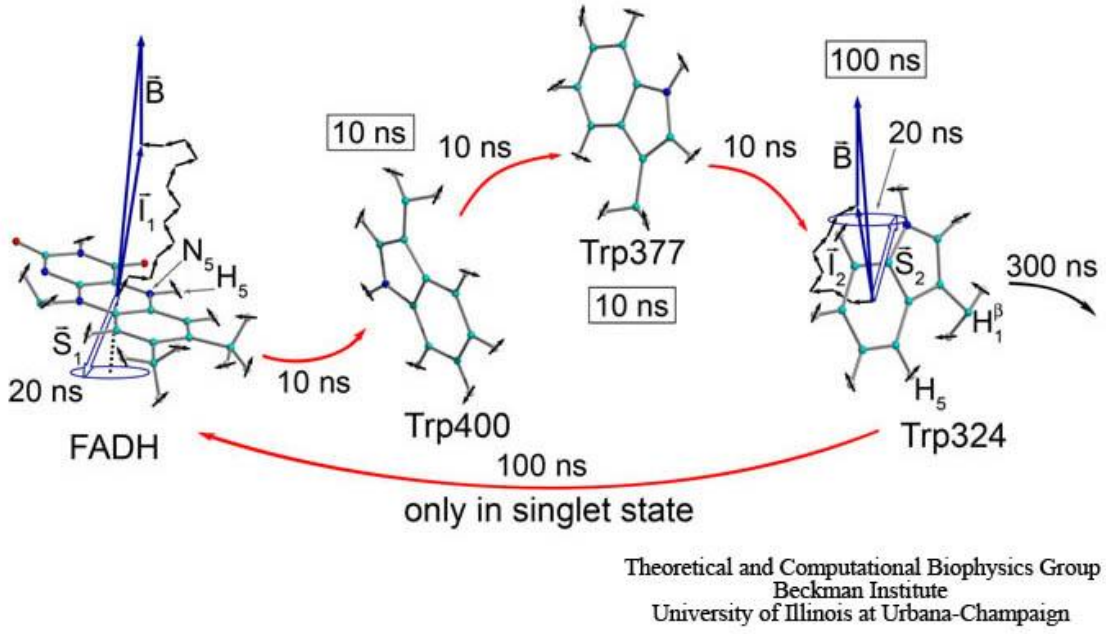
nearby aspartic acid, producing $FADH^+$. Once the electronically excited flavin is in the $FADH^+$ state, light-induced electron transfer is initiated. An electron first jump from the nearby Trp400 into the hole left by the excited electron in $FADH^+$, forming FADH + $Trp400^+$. An electron then jumps from Trp377 to Trp400, forming FADH + $Trp377^+$, and subsequently from Trp324 to Trp377, forming FADH + $Trp324^+$. Finally $Trp324^+$ becomes deprotonated to $Trp324_{dep}$, i.e., forming FADH + $Trp324_{dep}$, fixing the electron on the FADH cofactor. The protein cryptochrome is thought to be in its active (signalling) state when the flavin is in this FADH form. An external magnetic field can interact with each of the three radical pair states (FADH + $Trp400^+$, FADH + $Trp377^+$, FADH + $Trp324^+$) formed during the photoreduction process. (5.)



(Fig. 6.) Light-induced photocycle in cryptochrome. The signaling state of cryptochrome is controlled by the oxidation state of its flavin cofactor FAD, which exists in three interconvertible redox forms, FAD, FADH, and $FADH^-$. The FAD form is inactive (non-signalling) and accumulates to high levels in the dark. Blue light triggers photoreduction of FAD to establish a photoequilibrium that favors FADH over FAD or $FADH^-$. The semiquinone FADH state corresponds to the signalling state of the protein. Green light photons can further be absorbed by the radical FADH and shift the photoequilibrium to the fully reduced form ($FADH^-$), which is inactive (non-signalling). The FAD→$FADH^-$ and FADH→$FADH^-$ reactions involve an active FADH radical and, therefore, can be affected by an external magnetic field. The excited states of the flavin cofactor, FAD^* and $FADH^*$, colored gray, arise as short-lived intermediate stages of the cryptochrome photocycle. (5.)

Effect of the magnetic field:

The idea behind the magnetic field effect in cryptochrome activation reaction is illustrated in Fig. 7. Cryptochrome is brought to its active (signalling) state via the photoreduction process described above. However, cryptochrome could revert to its non-active form if ever the unpaired electron on FADH back-transfers to one of the three tryptophans. This back-transfer process is spin-dependent, as it can only take place if the spins of the two unpaired electrons on FADH and the tryptophan are in an overall singlet (antiparallel) state, rather than a triplet (parallel) state. The spins of the unpaired electrons precess about the local magnetic field, which consists of contributions from the surrounding nuclei as well as from the external magnetic field. As each of the electron spins precess, they change their orientation with respect to one another. For example, if the spins begin in a singlet (antiparallel) state, their precession will bring them out of alignment, introducing some triplet contribution. In this way, the presence of the external magnetic field can influence the precession of the electron spins and thereby influence the amount of time the spins spend in their singlet state. This, in turn, influences the probability for electron back-transfer and therefore the amount of time that cryptochrome spends in its signaling state. (5.)



(Fig. 7.) Shown here is a semi-classical description of the magnetic field effect on the radical pairs between FADH and tryptophan in cryptochrome. The unpaired electron spins (S_1 and S_2) precess about a local magnetic field produced by the addition of the external magnetic field B with contributions I_1 and I_2 from the nuclear spins on the two radicals. The spin precession continuously alters the relative spin orientation, causing the singlet (anti-parallel) to triplet (parallel) interconversion which underlies the magnetic field effect. Electron back-transfer from a tryptophan to FADH quenches cryptochrome's active state. However, this back-transfer can only take place when the electron spins are in the singlet state, and this spin-dependence allows the external magnetic field, B, to affect cryptochrome activation. (5.)

Involvement of superoxide radical:

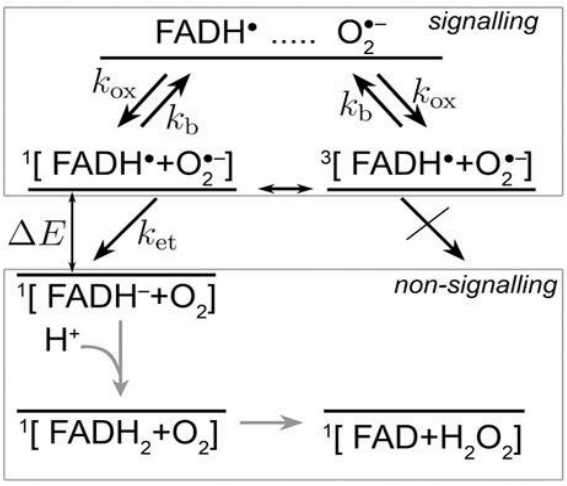
However cryptochrome's signalling state has a limited lifetime. Under aerobic conditions, the stable FADH molecule slowly reverts back to the initial FAD state as illustrated in Fig. 6. This process is not well understood and occurs on the millisecond time scale. The cryptochrome back-reaction attracted considerable attention recently due to indications that it may be the key link to avian magnetoreception. In the course of the back-reaction a radical pair is formed between flavin and an oxygen molecule. This reaction has some favourable properties these make it more appropriate for the experimental findings. Both O_2 and its reduced form superoxide radical $O_2^{\cdot -}$ are paramagnetic, and devoid of the hyperfine couplings, which is likely to lead to higher sensitivity against weak magnetic fields, because of the magnetic nuclei are highly asymmetrically distributed between the 2 radicals and that such radical pairs may be especially sensitive to radio frequency fields too. (2, 7.) In addition, such a radical pair (where one radical has no hyperfine coupling) would be consistent with studies on the effects of weak radio-frequency oscillating magnetic fields on migratory bird orientation. Ritz and co-workers not only found that appropriate orientation behaviour depends on the strength and angle of the oscillating field, but also that the minimum field strength necessary to disrupt orientation depends on the frequency of the oscillating field in a resonance-like behaviour that would be predicted by such a radical pair. (5.) To simplify this case entanglement only exists in time scale much shorter than the lifetime of the radical pair, and quantum mechanical calculation (7.) showed that a substantial part of

all separable states can account for an angular dependence that is as high as (or even higher) than for the singlet state. This means that the radical-pair entanglement does not seem to be a necessary ingredient for a chemical compass based on FADH•-O2•−. However, the hypothesis that an oxygen molecule is involved in magnetoreception still needs to be verified experimentally.

At a first glance, the involvement of superoxide, O_2^-, in the magnetic field dependent back-reaction of cryptochrome seems rather controversial. It seems odd that an organism should rely on a toxic substance for a sensory mechanism. However, one should note that superoxide arises naturally in organisms, and is well controlled by superoxide dismutase, which keeps the concentration of superoxide low. This low concentration level, though, is key to the suggested mechanism as the reaction back to the non-signalling state of cryptochrome should be slow, i.e., take about 10 ms. Such slow rate of diffusion-controlled encounter is ensured through the low O_2^- concentration. At a concentration of $[O_2^-]$=3 nM, which is tolerable to an organism, the formation of FADH+O_2^- is estimated to take about 1.1 ms, which is indeed the time needed for the suggested mechanism to function optimally.

The back-reaction:

The back-reaction in cryptochrome likely involves the superoxide radical O_2^-. The superoxide radical O_2^-occurs widely in nature and can be obtained as the product of the one-electron reduction of molecular oxygen (O_2). $O_2^-$is toxic to cells and under physiological conditions is available only in nM-ÂµM concentrations, which is well controlled by an enzyme, superoxide dismutase. The reaction of the semiquinone FADH state of the flavin cofactor in cryptochrome with O_2^- is schematically shown in Fig. 8. The molecular oxygen radical O_2^-enters the molecular pocket in cryptochrome, depicted in Fig.8, with a rate constant k_{ox}, creating a radical pair [FADH+O_2^-], which can be either in a singlet or a triplet state, as denoted by ^{1}[…] or ^{3}[…], respectively. If the radical pair is found in its singlet state, the electron from the O_2^- radical should transfer to the FADH radical, since the energy of the ^{1}[$FADH^-$ +O_2] state is lower than the energy of the ^{1}[FADH+O_2^-] state. The electron transfer is only possible from the singlet state of the radical pair, the corresponding rate constant being depicted in Fig. 8 as k_{et}. The triplet state ^{3}[$FADH^-$+O_2] can only produce $FADH^-$ after it is converted to the singlet state ^{1}[$FADH^-$+O_2]. (5.)



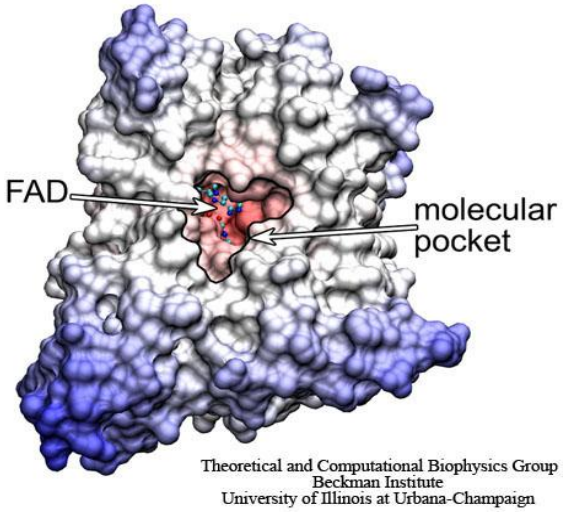


Fig. 8. Here is a schematic presentation of the postulated reaction scheme involving the flavin cofactor FADH in cryptochrome and a molecular oxygen radical (superoxide) O_2^-. Superoxide enters the molecular pocket of cryptochrome with a rate constant k_{ox}, forming a radical pair [FADH + O_2^-], which is found in a singlet (25 %) or a triplet (75 %) state, denoted by ^{1}[…] or ^{3}[…], respectively. An external magnetic field as well as the hyperfine coupling interaction brings about an interconversion between the singlet and the triplet states of the radical pair. If the radical pair is in its singlet state, the electron from the O_2^-radical can transfer to the FADH radical, forming the singlet ^{1}[$FADH^-$+O_2] state, which has lower energy than the initial ^{1}[FADH+O_2^-] state; the corresponding electron transfer rate constant is k_{et}. The electron transfer is not possible from the triplet state of the radical pair, due to spin conservation during the transfer. The radical pair can separate, i.e., the O_2^- radical escapes (with a rate constant k_b) from the molecular pocket before electron transfer occurs, leaving cryptochrome then in its signalling state. The non-signalling $FADH^-$ state is transformed to the FAD resting state, possibly by subsequent protonation and release of a hydrogen peroxide molecule. (5.)

Effect of the magnetic field:

The external magnetic field and the hyperfine interaction affect the interconversion between the singlet and the triplet states of the radical pair in a manner that depends on the orientation in the Earth magnetic field. Once the FAD cofactor is reduced to the $FADH^-$ state, cryptochrome stops signalling, because the reaction FADH+O_2^-→$FADH^-$+O_2 is considered irreversible. However, before this reaction occurs, the radical pair may separate, namely, if the O_2^- radical escapes from cryptochrome's molecular pocket, leaving cryptochrome then still in its signalling state. The escape reaction is governed by the rate constant k_b, as depicted in Fig. 8, and can occur equally likely from either the singlet or the triplet state of the radical pair, as depicted in Fig. 8. Thus, cryptochrome remains in its signalling state until another O_2^- radical arrives, and the FADH radical gets another chance to be reduced. The separation and re-encounter of O_2^- delay the magnetic field-dependent reaction, shifting it to the millisecond time scale, i.e., the time scale relevant for biological signalling.

Computational studies of the radical pair-based back-reaction in cryptochrome in a weak (i.e., the Earth's) external magnetic field demonstrated that the duration of cryptochrome's FADH+O_2^-→$FADH^-$ +O_2 reaction can be changed significantly. Moreover it was shown that the suggested reaction can act as an inclination compass by demonstrating that a field of 0.5 G produces effects that vary significantly during reorientation of cryptochrome.

Another argument, that speaks for the suggested reaction is its robustness. Indeed, the suggested back-reaction is much simpler than the magnetic field-dependent reaction in cryptochrome activation process and, therefore, is expected to function more reliably in a weak magnetic field. (5.)

Possible neural connections, visual representation:

Neural activity during magnetic orientation behaviour co-localizes with cryptochrome expression in retinal ganglion cells in a night-active migratory bird, whereas no such co-localization occurs in nonmigratory birds or during daytime. However, it is not known whether this is due to a link between crypto chromes and magneto reception or simply a link between cryptochromes and photoperiodic behaviour that is associated with migration. Several lines of evidence have indicated a link between magnetoreception and the visual system. Electrophysiological responses to magnetic fields have been detected in several parts of the avian brain that receive projections from the visual system. For example, the nucleus of the basal optic root (nBOR) in pigeons receives projections from retinal ganglion cells, and some neurons in the nBOR and optic tectum respond to directional changes in the ambient magnetic field. The amplitude of the responses in the nBOR depended on the wavelength of the light entering the eye and responses to magnetic fields in both locations disappeared when the

optic nerves were cut. Several studies have also indicated a link between magnetoreception and the pineal gland. Electrophysiological recordings from pigeon pineal cells revealed units that were responsive to gradual changes in Earth-strength magnetic fields. Responses were reduced, but not abolished, when the optic nerves and other sources of input to the pineal gland were severed, which implies that one source of magnetic sensitivity is in the pineal gland itself . A study with newts also revealed that the magnetic direction that newts orientated towards shifted when the pineal complex was illuminated with light of a specific wavelength, whereas no such response was elicited when the light illuminated the eyes alone. (1.)

So we are look for the signalling molecule in the eye. Calculations showed that only one rotational degree have to be constrained to function as a magnetoreceptor, so any membrane associated molecule suitable.

In mathematical terms, the vision-based compass in birds is characterized through a filter function, which models the magnetic field-mediated visual signal modulation recorded on the bird's retina.

To model the effect of a field-dependent radical-pair process on an animal's vision one needs to specify how such a process interacts with the visual pathway. For the purpose of illustration we assume that the radical-pair process affects the sensitivity of the light receptors in the eye. This modulation of sensitivity will result in a response pattern that varies over the hemisphere of the eye. We model the eye as displayed in Fig. 9 as a pinhole camera with an infinitesimal opening at O'. The retina is assumed to be a perfect sphere with the light receptors oriented normal to the sphere (c.f. *z*1 and *z*2 in Fig. 9). The eye is assumed to be cyclopean, i.e., in the centre of the head. The direction of the central line connecting O and O', henceforth, will be referred to as the viewing or head direction. The unmodified signal *s* is represented by an integer in the range 0–255. We show how vision would be modulated if the bird was looking at a uniformly gray screen (*s*=127) measuring 62° x 62°. The modified signal *s*' is determined according to a linear transduction formula:

$$\mathbf{s'(\theta)=127+255x[(\Phi_T(\theta)-\Phi_{gauge})M],}$$

where Φgauge represents the triplet yield averaged over all angles and where *M* is an amplification factor. We have chosen *M* =4.

The patterns that describe the modification of view for different head orientations are collected in Fig. 10. The numbering "0" to "180" refers to the angles of the different viewing directions with respect to the geomagnetic field vector. The modulation pattern for a bird looking parallel to the magnetic field lines ("0" in Fig. 10) is essentially a disk in the centre of vision. We found it convenient, for the sake of illustration, to choose parameters such that the disk is darker than the surroundings. Biologically, this could correspond to a decrease of sensitivity of the receptors in this region. However, the magnetic compass would work similarly if receptor sensitivity is increased rather than decreased. (3.)

By the way, we have to remember, it is a highly simplified model (the shape of eye not perfectly circular, birds have two eyes, we do not know the receptor density in the retina...) and the modulation of the modulation of the brightness is also a hypothesis, just for the example. Sensing of the magnetic field can have a totally separated neural processing from the visual information (Fig. 11.).

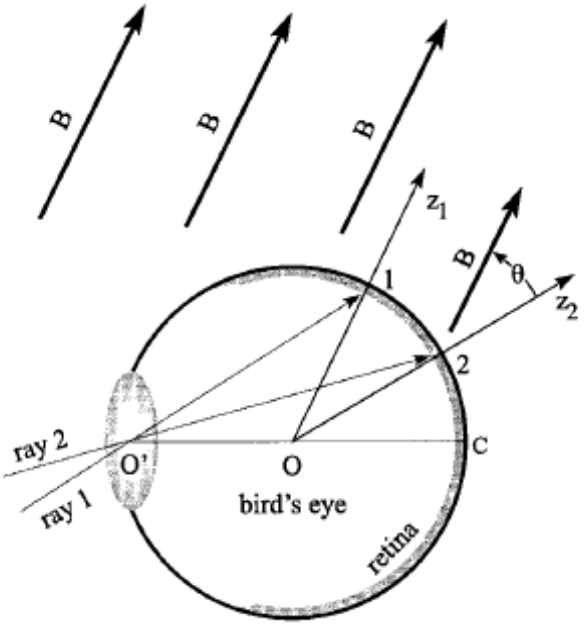


Fig. 9: (3.) Eye model used for the calculation of visual modulation patterns. Rays 1 and 2 enter through an infinitesimal hole at O′ and are projected onto a spherical retina. The receptor molecules are assumed to be oriented normal to the retina surface (directions z_1 and z_2), thus forming different angles with the direction of the magnetic field vector.

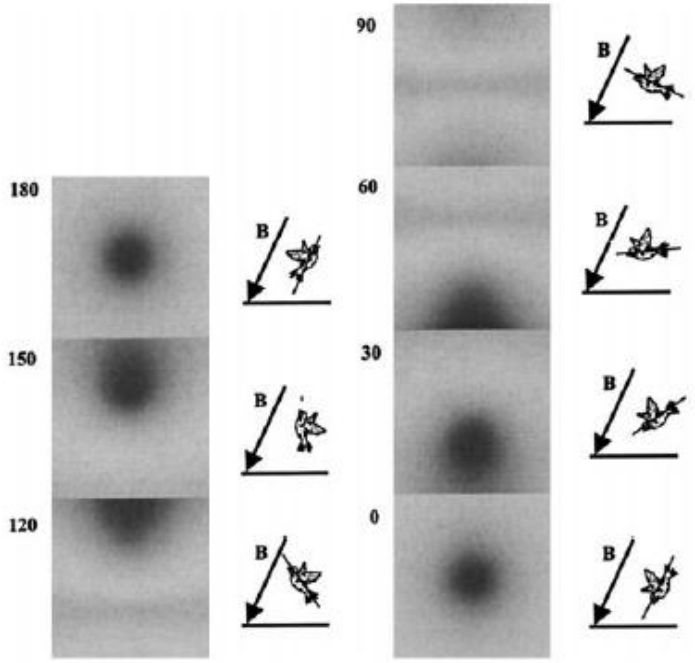


Fig. 10: (3.) Visual modulation patterns through the geomagnetic field (0.5 G) for a bird looking into different directions at angles 0°, 30°, 60°, 90°, 120°, 150°, and 180° with the magnetic field vector. The patterns have been evaluated assuming radical-pair receptors with anisotropic hyperfine couplings arranged in the eye model The schematic illustrations next to the modulation patterns indicate the corresponding direction into which a bird would be flying at Urbana-Champaign (geomagnetic field inclination of 68°).

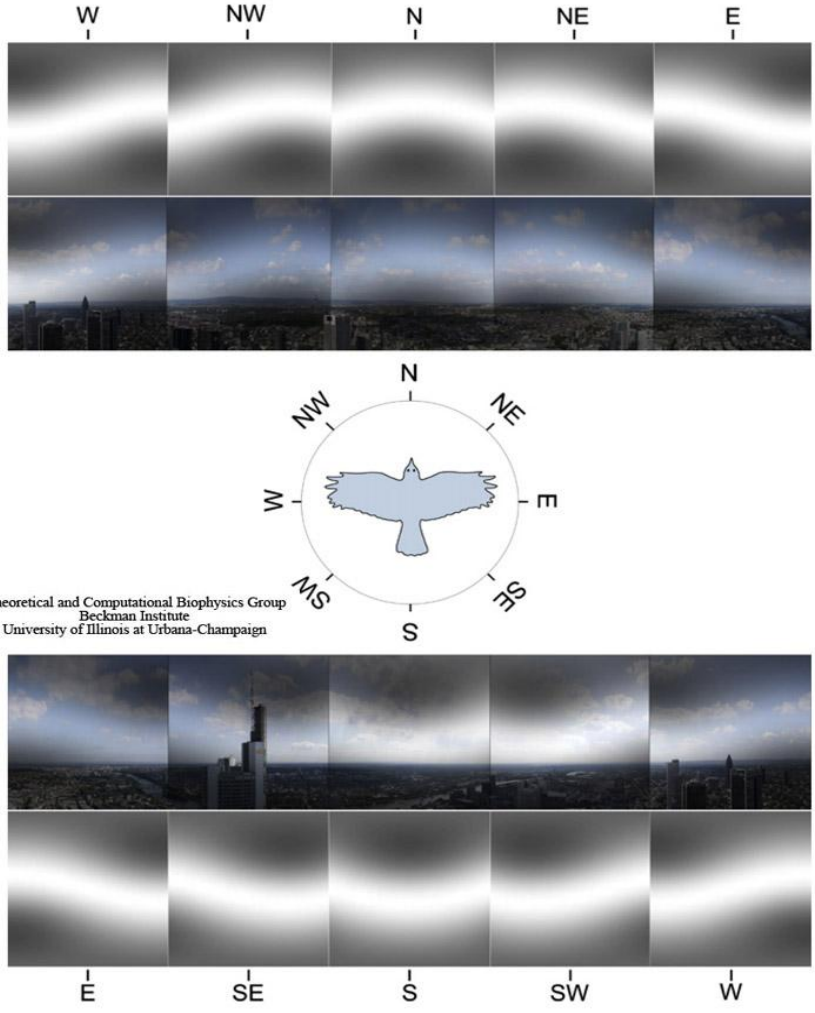


Fig. 11. Here is a panoramic view of Frankfurt, Germany. The image shows the landscape perspective recorded from a bird flight altitude of 200 m above the ground with the cardinal directions indicated. The visual field of a bird is modified through the magnetic filter function. For the sake of illustration we show the magnetic field-mediated pattern in greyscale alone (which would reflect the perceived pattern if the magnetic visual pathway is completely separated from the normal visual pathway) and added onto the normal visual image the bird would see, if magnetic and normal vision uses the same neuronal pathway in the retina. The patterns are shown for a bird looking at eight cardinal directions (N, NE, E, SE, S, SW, W, and NW). The geomagnetic field inclination angle is 66Â°, being a characteristic value for the region. (5.)

Summary:

Many animals (for example birds, fish, and insects) feel the magnetic field of the Earth and use this information in navigation, for example during migration. Anisotropic hyperfine coupling based radical pair mechanism; a photochemical reaction is one of the main candidates of the magnetoreception. For functioning as a molecular compass a protein in the retina of some animals, the cryptochrome is a potential applicant. It satisfies the theoretical constraints and the behaviour experimental results. The last 40 years of experimental and theoretical research in physics, chemistry, anatomy, neurobiology and ethology gave fundamental improvements to this field, but the basic questions still remain and wait to be solved and the hypothesises to be proved. So there is a lot of work left if we want to understand this, fascinating and unsolved sensing mechanism.

References:

1. Sönke Johnsen and Kenneth J. Lohmann, THE PHYSICS AND NEUROBIOLOGY OF MAGNETORECEPTION, NATURE REVIEWS, NEUROSCIENCE VOLUME 6, SEPTEMBER 2005

2. Chemical magnetoreception in birds: The radical pair mechanism; Christopher T. Rodgers and P. J. Hore; PNAS, January 13, 2009 vol. 106 no. 2;

3. A Model for Photoreceptor-Based Magnetoreception in Birds; Thorsten Ritz, Salih Adem, and Klaus Schulten; Biophysical Journal Volume 78 February 2000

4. Magnetic compass of European robins, Wofgang and Roswitha Wiltschko; Science, 7th, April, 1972

5. www.ks.uiuc.edu/Research/cryptochrome/

6. Chemical compass model of avian magnetoreception, Kiminori Maeda1, Kevin B. Henbest1, Filippo Cintolesi, Ilya Kuprov, Christopher T. Rodgers, Paul A. Liddell, Devens Gust3, Christiane R. Timmel1 & P. J. Hore2, Vol 453, 15 May 2008, nature06834

7. Quantum control and entanglement in a chemical compass, Jianming Cai, Gian Giacomo Guerreschi, and Hans J. Briegel.

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