The Radical Pair Mechanism of Animal Magnetoreception

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Introduction

- Magnetic fields do not interact significantly with biological materials. Unlike most stable biological polymers, radicals have an unpaired electrons which make them susceptible to magnetic fields due to a quantum property known as *spin.*
- The ***radical pair mechanism*** (RPM) is a model for animal magnetoreception that takes into account reliance on light for orientation and the polarity compass phenomenon(***Fig. 1***).
- ***Cryptochrome***, a circadian protein, is the putative magnetoreceptor in some organisms that exhibit magnetosensitive behaviours. It has been studied *in vitro*, in situ in neuronal cells and in knockout genetic models of *Drosophila*.

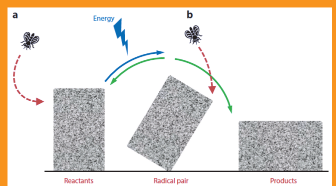
Quantum AND Biology?

BIOLOGY:

- Some species can navigate using the Earth's magnetic field as a guide (***Fig. 2&3***).
- This has been proven to be a light-dependent phenomenon, and therefore is not simply analogous to a simple magnetic compass as once thought.

QUANTUM CHEMISTRY:

- Well-studied in chemistry, RPM relies spin-correlated radicals in which their unpaired electrons experience a local magnetic field as well as the external magnetic field applied to the system. Their spin-state mixing is affected by the these two magnetic field components and other factors to affect reactivity.



- When photoexcited, cryptochrome is reduced, creating a radical pair. Unpaired spins undergo ***singlet-triplet mixing*** naturally and can also be modulated via the presence of external applied magnetic fields. The resultant yields of singlet or triplet states affects reactivity of the radicals and can cause alternative spin-selective reaction pathways to become more favourable [1]

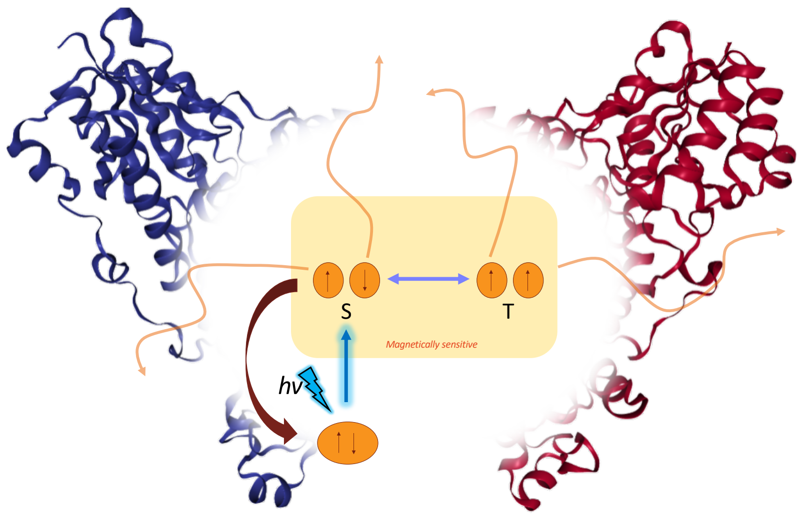


Figure 1 ***Proposed depiction of the radical pair mechanism of animal magnetoreception in cryptochrome***
Excitation of FAD cofactor by a single photon of light excites a singlet precursor pair and generates a radical pair. Yield in each quantum state can be modulated by an applied, external magnetic field. Incident light, denoted by 'hv', on the FAD cofactor excites a singlet precursor pair to the excited state (blue arrow), forming the radical pair. The unpaired electrons interchange between singlet and triplet quantum states in a magnetically dependent manner (depicted by a purple double-headed arrow), which alters their state-dependent chemical reactivity. The back reaction (recombination), depicted by a curved maroon arrow, only occurs when unpaired electrons reencounter in the singlet state. If the radicals in the pair do not reencounter in the singlet state, they escape the local solvent cage into the environment (depicted by undulant orange arrows) to form alternate reaction products. Yields of these products could provide a biological basis for sensing.

Aims

- To develop an '*In vivo*' alternative to *in vitro* studies of CRY protein magnetic field effects outside the native environment, via heterologous expression.
- To use this to identify the mutations that optimise or destroy these magnetic field effects.

Methods

- Express CRY variants in *Escherichia coli (E. coli*)
- Phenotypic growth and toxicity in light and dark conditions, under an applied external magnetic field.
- Introduce mutations at conserved or particularly critical residues via PCR site-directed mutagenesis and observe effects.
- *In silico* molecular dynamics simulation of mutants

Background research

In *Erithacus rubecula* [4]: Response to magnetic fields only significant when exposed to blue light wavelengths; *polarity independent.*

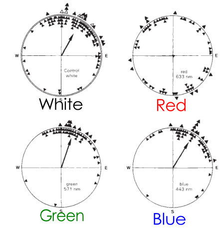


Figure 2: Mean headings of *E. rubecula* (n=11; each triangle representing one of 3-6 headings per individual), and the average denoted by the length and direction of radial vector arrow from origin.
Wiltschko et al. *Nature*, **1993**, 364(5), 525-527

In *Drosophila* [2,3]: experiments show natural magnetic sense in fruit flies and can be trained to demonstrate affinity or avoidance of magnetic fields.

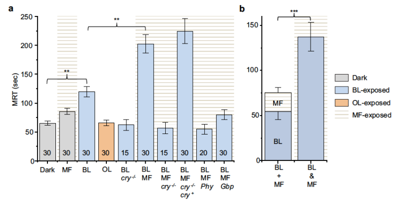


Figure 3: *Seizure duration of third instar Drosophila larvae, measured as mean recovery time (MRT) from electric shock under various conditions of blue/orange light and with/without applied magnetic fields.* BL & MF is significantly potentiated beyond additive effects of each independent condition alone.
Marley *et al. Sci. Rep.* **2014** 4 : 5799, DOI: 10.1038/srep05799

Impacts

- Determine the feasibility of CRY-based opto-/magneto-genetic tools for use as a experimental or therapeutic agents.
- Evidence of non-trivial quantum effects in a macroscopic biological process

References

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2 Hore PJ & Mouritsen H (2016) The Radical-Pair Mechanism of Magnetoreception. *Annu. Rev. Biophys*. **45**, 299–344.
3 Wiltschko R, Thalau P, Gehring D, Nießner C, Ritz T & Wiltschko W (2015) Magnetoreception in birds : the effect of radio-frequency fields. , 1–6.
4 Marley R, Giachello CNG, Scrutton NS, Baines RA & Jones AR (2014) Cryptochrome-dependent magnetic field effect on seizure response in *Drosophila* larvae. *Sci. Rep.* **4**, 1–4.

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