Magnetosensitive biomolecules

Simulations of Supramolecular Biological Systems

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In Short

- Cryptochrome interaction partners
- Cryptochrome/membrane interaction
- Spin dynamics and magnetic field interaction of radical pairs in cryptochrome
- Electron transfer processes in protein structures

In the last two decades, the question of how night-migratory songbirds find their way on longer migrational journeys has come closer to a definitive answer. The migratory sense of birds is thought to be a light activated process, and upon blue light absorption by a photoreceptor cryptochrome an electron transfer from a tetrad of tryptophan residues to the flavin adenine dinucleotide cofactor produces a radical pair whose subsequent reactions are thought to be sensitive to the Earth's magnetic field. The existence of the electron transfer and radical pair and the radical pairs importance on the magnetic sensibility of cryptochrome 4 (Cry4) proteins was unveiled in a recent article in Nature [1].

Despite the recent groundbreaking discoveries, there are still some unanswered questions, on a microscopic level especially regarding interactions with key interaction partners of the European robin cryptochrome 4a (ErCry4a) found in the last years [2,3]. Specifically the two interaction partners that have been suggested are long-wavelength sensitive opsin (LWO) or the α unit of the cone-specific heterotrimeric G protein. Neither of the suggested interaction partners have a known crystal structure, hence the first aim of the project is to successfully reconstruct the interaction partners computational models using either homology modeling, or in case of low sequence identity, AlphaFold [4].

Another possible interaction partner of cryptochrome are membranes. It is therefore obvious to also investigate the possibility of cryptochromes binding to a membrane. ErCry4a has no transmembrane domains, such that insertion into a membrane can be excluded. However, an association of ErCry4a with the polar surface of the cell membrane is probable. Electrostatic interactions between ErCry4a fragments and negatively charged lipids (e.g. phosphatidylserine which is commonly found in the cytoplasm-facing leaflet of cell membranes) represent one of the possible interaction pathways; to support this rationale, a preliminary study has established surface charge densities of ErCry1 [5] and showed that some protein fragments have a positive surface charge density, see Fig. 1.

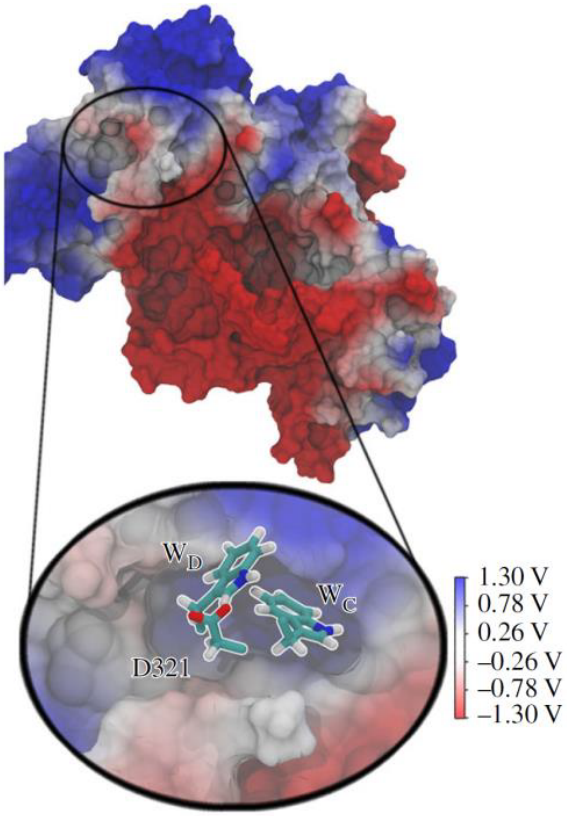

***Figure 1:** Surface electrostatic potential of ErCry1a.*

Furthermore, in order to connect the radical pair mechanism to the overall signaling of the ErCry4a protein, the radical pair must exist. In Xu et al. [1] it was shown that a radical pair existed within the ErCry4a protein at a distance of 16 Å, and a possible electron transfer path was documented. The overall electron transfer pathway was only briefly studied theoretically in the study and will be studied in much more detail in the coming year, in particular it will be studied whether the pathway can be blocked by mutating the residues responsible for the electron transfer pathway, see Fig 2B.

Lastly, it is imperative to also investigate the influence of an external magnetic field on the

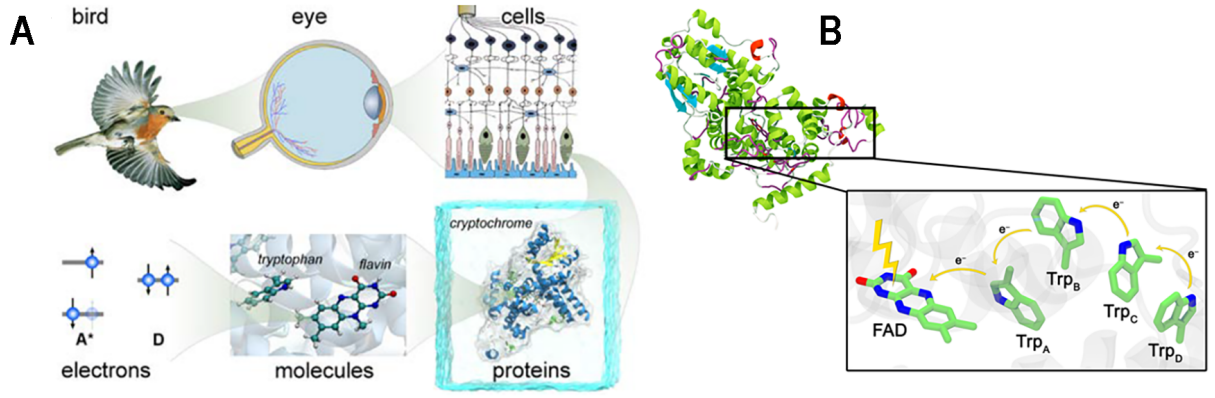

Figure 2: *A: Avian magnetoreception is a multiscale problem. B: FAD becomes a radical upon photoabsorption through electron transfer from a nearby tryptophan residue which causes a cascade of electron transfer reactions between three further tryptophan residues, shown in green*

radical pair of the ErCry4. In particular, this can be investigated by calculating the quantum yield of the signaling state in individual cryptochrome molecules using previously developed spin dynamics simulation techniques. Briefly, the coherent interconversion of the singlet and triplet electronic states of flavin-tryptophan radical pairs will be modeled by means of a stochastic Liouville equation including spin-dependent recombination reactions and spin-independent reaction steps. The aim is to make the spin dynamics simulations as realistic as possible by including information derived from detailed in vitro study of the magnetic sensitivity of cryptochromes [1]. All relevant magnetic interactions (hyperfine, exchange, dipolar) will be included. The outcome will be a set of data for the dependence of the magnetic signal strength on the direction of an Earth-strength ($\sim$50 μT) magnetic field for a range of plausible reaction rate constants and spin relaxation times.

A more general approach requires the development of the stochastic Schrödinger equation method [6]. Stochastic fluctuations of internal magnetic interactions (used to model spin relaxation) will be replaced by the Zeeman interactions of the electron spins with noise-modulated, broadband radiofrequency fields. Preliminary calculations suggest that this is feasible and that efficient trace-sampling and time-propagation techniques will allow modeling of realistic flavin-containing radical pairs. The aim here is to identify combinations of static and radiofrequency magnetic field conditions that have the power to discriminate between the various cryptochrome-based radical pairs that have been proposed as possible magnetic sensors, and to define their orientations within cells in the retina. The simulations and their predictions will be refined in an iterative process using feedback from experiments. It is anticipated that the results will also be applicable to electrophysiological measurements.

By performing the computations planned, we strongly believe that we will come closer to answering part of the overall scheme presented in Fig. 2A, which, if true, gives the answer of how birds use the magnetic field of the Earth on their long migratory journeys.

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More Information

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