

## SUMMARY & SPECIFIC AIMS

The exposure of our species to magnetic fields has steeply increased with the advent of wireless technology. Neither the health effects nor the physiological mechanism, if any, behind magnetosensitivity in humans are well established. Interestingly, vertebrates (such as birds and turtles) and invertebrates (such as migrating butterflies) alike navigate for thousands of miles partly guided by Earth's magnetic field [1] – which is weaker than the field in the proximity of a cell phone [2].

The leading model to explain magnetosensitivity is rooted in the well-understood fact that a magnetic field can alter the products of a class of light-dependent chemical reactions involving unpaired electrons [3]. This could explain, in principle, how the effect of a magnetic field could be 'physiologically measurable': an organism would perceive a magnetic field to the extent that it would perceive variations in the physiological concentration of chemical compounds. Previous experimental evidence suggests that this type of **chemical magnetosensitivity may be universal across many species**, as very similar behavioral and genetic signatures have been consistently observed in organisms ranging from birds to fish and insects [1]. Light-dependent reactions mediating magnetosensitivity are believed to take place inside cryptochrome (CRY), a photoreceptor protein, which is also expressed in fungi, sponges, algae, plants, amphibians, and mammals – including humans. Incidentally, CRY is thought to be involved in the alleged impact of radio-frequency fields on human health [4].

Despite extensive studies on magnetosensitivity at very distinct length scales – namely, ensembles of *in vitro* molecules vs. genetic and behavioral assays with the whole organism –, the lack of *in vivo* experiments at chemically relevant length scales prevents the establishment of a direct link between underlying mechanism and organismic physiology. Here I propose to bridge this gap by **investigating responses to magnetic stimuli in a live organism**, by combining: **advanced control methods**, typically used in physics experiments on quantum sensing in which I was trained as a graduate researcher at the Massachusetts Institute of Technology (MIT); with **single-molecule and optical tomography techniques** well-adapted to biological settings and extensively used in my host lab at Stanford University. This will be accomplished following two aims:

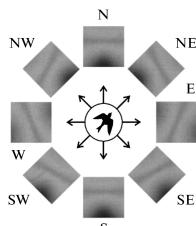
- 1. To establish optimal field conditions yielding magnetosensitivity in *in vitro* CRY – with unprecedented single-molecule resolution.** With sub-diffraction resolution, CRY will be photoexcited in a total internal reflection microscope [5] in which the image acquisition is synchronized to an applied magnetic field. Recordings of single-molecule CRY fluorescence intensity, a proxy for magnetosensitivity in this protein, will be correlated to intensity, frequency and direction of the external field; and to different laser wavelengths (sub-aim **1a**). I expect the resulting novel magnetosensitivity 'dependency map' will be consistent with findings from behavioral and ensemble *in vitro* studies (ex.: blue light activates magnetosensing [6]). In addition, working at the single-molecule level will enable me to confirm or refute predictions of the model which, to date, remain experimentally inaccessible, such as the magnetosensitivity dependence on field direction [7] (sub-aim **1b**).
- 2. To localize physiological CRY expression inside fruit fly larvae, and identify its magnetosensitivity signatures *in vivo*.** The link between *in vivo* CRY functioning and organismic physiology can be investigated by combining lattice light sheet microscopy [8], a high-resolution, low-phototoxic 3D optical tomography technique, with synchronous magnetic stimuli. I will photoexcite and image fruit fly larvae, which are CRY-dependent magnetosensitive [9], to determine where CRY is physiologically expressed (sub-aim **2a**). I will subsequently measure magnetosensitive signatures of CRY inside the larvae by investigating, for the first time *in vivo*, whether CRY fluorescence intensity is modulated by different magnetic fields (sub-aim **2b**); relevantly, I will excite the organism with fields shown to yield strong magnetoresponses in single-molecule CRY.

Combining single-molecule understanding of (light-dependent) CRY magnetosensitivity (aim 1) with the signatures of its physiological expression *in vivo* (aim 2) will **unveil the fundamental chemical mechanism thought to underlie magnetic navigation across a wide range of species**. This knowledge will make it possible to engineer ultrasensitive biologically-inspired magnetoprobes, which is advantageous as nature itself has taken care of selecting winning sensing strategies. Potential sensor applications range from strategic navigation to improved healthcare magnetic scanners. Moreover, this work will pave the way to assess whether the magnetosensitivity mechanism behind the behavior of flies (at least), among others, can explain the effects of exposure to magnetic fields on human health, if any. Finally, and crucially, experiments such as the ones proposed here will constitute a rigorous trial of the premise that quantum physics can inform biology at the nanoscale.

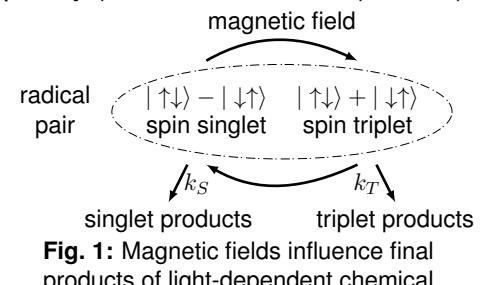
## SIGNIFICANCE & RELEVANT TRAINING

There is a striking parallel between the considered model of chemical magnetoreception and the goals of the emerging field of quantum sensing and control. Quantum sensing is based on the experimental ability to maintain a ‘quantum bit’ (ex.: an electronic spin in diamond) in an out-of-equilibrium state, i.e. shielded from the environment, for long enough so that it can act as a precise quantum sensor. The quantum character of the sensor typically enhances the measurement sensitivity. My work as a doctoral student at MIT unveiled a protocol to extend the quantum character of such an electronic spin in diamond. As decoherence effects were mitigated by the application of tailored controls, the spin sensor could yield information on magnetic fields one order of magnitude weaker than the Earth’s [10]. The model behind chemical magnetosensitivity, in turn, postulates that a local out-of-equilibrium state should be sustained in the magnetoreceptive organism, and for a long enough duration, such that a magnetic field can influence light-dependent chemical reactions containing unpaired electrons, also known as ‘radical pairs’ [3]. Such a radical pair will precess differently in the presence of different magnetic fields, and thus act as a sensitive magnetometer, in the exact way that a quantum bit in diamond does: by having its spin state changed by a prescribed amount determined by field strength, frequency and direction. The final spin state (singlet or triplet) of the radical pair as it loses its quantum character is presumed to influence the resulting chemical products of a chain of reactions [Fig. 1]. Nanotech chemically engineered sensors have been demonstrated using this very principle [11, 12]. Importantly, for both the diamond spin and the radical pair, this effect is measurable even if hyperfine and magnetic (Zeeman) interactions are many orders of magnitude smaller than the thermal energy per molecule as **the sensor is not in thermal equilibrium with its environment**. Since synchronized experiments on quantum sensing in diamond, such as the one I built at MIT, are customarily run at room temperature and in a bulk crystal, it is conceivable that nature optimized a biological sensor to work under similarly messy physiological conditions. In a conservative estimate, to sense the geofield, spins must have relaxation times  $\gtrsim 0.7 \mu\text{s}$ , value corresponding to the inverse of the electronic Larmor precession frequency ( $\sim 1.4 \text{ MHz}$  for a  $50 \mu\text{T}$  field).

To date, cryptochromes (CRY) is the only animal photoreceptor known to sustain radical pairs [7]. Broadly expressed and implicated in circadian rhythm regulation [13], CRY has also been directly linked to magnetosensitivity in many organisms (ex.: CRY knock-out causes loss of magnetosensitivity [9]). Spin-relaxation times of the radical pair, for ensemble measurements on CRY (respectively, on a CRY-family protein), have been reported to be  $\sim 10 \mu\text{s}$  at  $1^\circ\text{C}$  [14] ( $\sim 1 \mu\text{s}$  at room temperature [15]); comparably, spin-relaxation times (i.e. no controls applied) of the diamond spin are on the order of a couple of  $\mu\text{s}$  [10]. In addition, room-temperature magnetosensitivity of *in vitro* CRY for Earth-strength fields has been measured [16]. These results support the hypothesis that, *in vivo*, radical pairs in CRY might be coherent for long enough to sense the magnetic field of the Earth; in other words, the geofield might indeed change the final chemical products of a chain of light-dependent reactions occurring within CRY. Presently, it is only speculated how animals could convert an altered physiological concentration of chemical compounds into field-tracking information. For example, it is thought that birds could effectively ‘see’ magnetic field lines if chemical concentrations modulate the light sensitivity in the retina (where CRY is found) [Fig. 2]. Unveiling the full mechanistic pathway, from molecular CRY magnetosensitivity to navigation behavior, will require, as a first step, to **image CRY and CRY-magnetosensitive organisms, while synchronously probing function with applied magnetic fields**.



**Fig. 2:** Putative visual modulation patterns that the Earth’s magnetic field may induce in the retina of a bird flying through the cardinal directions. From [17].



**Fig. 1:** Magnetic fields influence final products of light-dependent chemical reactions involving radical pairs.

I bring my unique quantum physics background to Prof. Prakash’s lab at Stanford University, which focuses on organismic biophysics, with the goal to uncover new mechanisms for sensing, actuation and computation in animals in different branches of the tree of life (including insects). The lab has expertise to culture, manipulate (molecularly and physically) and build behavioral assays for fly lines, besides having access to local fly facilities. Furthermore, I am developing state-of-the-art optical imaging tools which will allow me to perform both single-molecule, and *in vivo* experiments. The work that I propose to carry out, thus, lies at the interface between the chemical-physics of magnetosensitivity, and its physiological expression in an organism. I will implement quantum sensing methods for excitation and control, while reading out results using quantitative imaging methods.

I articulate below the plan to develop my two research aims. The paragraphs that follow have been organized to reflect the **significance** and **innovation** for each aim.

## AIM 1: TO ESTABLISH OPTIMAL FIELD CONDITIONS YIELDING MAGNETOSENSITIVITY IN IN VITRO CRY – WITH UNPRECEDENTED SINGLE-MOLECULE RESOLUTION

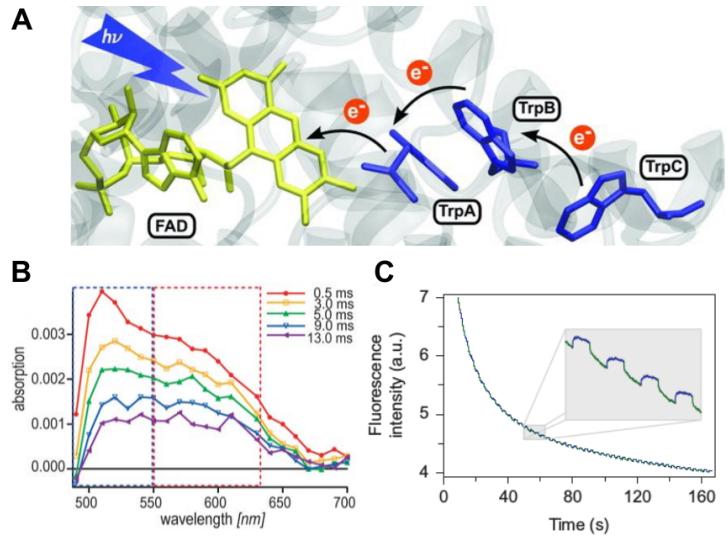
**Rationale.** Transient-absorption techniques have been very successful in elucidating the photophysics of ensemble CRY. It is now known that blue light [Fig. 3B] excites the flavin adenine dinucleotide (FAD) co-factor bound to CRY, initiating electron transfers along a chain of tryptophan residues [Fig. 3A]. A radical pair is eventually formed, having FAD and one tryptophan as hosts [17]. Spectral absorption and emission bands, however, remain unchanged as the protein is observed in bulk or with single-molecule resolution. The spin physics I am interested in, on the other hand, strongly depends on the local surroundings of each molecule. Similarly, ensemble magnetosensitivity cannot unveil how a molecular process reacts to magnetic field direction, as the signal from many tumbling molecules will wash out angle-specific information. To address these limitations, I will establish factors influencing magnetosensitivity in CRY with single-molecule resolution. Specifically, I will monitor how its fluorescence intensity changes as magnetic fields of different strengths, directions and frequencies are applied. Fluorescence intensity, while probably not the physiological quantity used by organisms to track fields, has been observed to directly reflect magnetic field sensing in CRY components [Fig. 3C]. I aim to determine the optimal magnetic field characteristics yielding strong magnetoresponses; sweet spots in such a magnetosensitivity dependency map will eventually be used as a guide to measure physiological magnetoresponses *in vivo*.

**Experimental strategy & preliminary results.** Purified (fly) CRY, initially in solution, will be photoexcited in a **total internal reflection fluorescence microscope** [5] **in which light excitation is synchronized to an applied magnetic field**. Recordings of CRY single-molecule fluorescence intensity will be correlated to intensity, frequency and direction of the external field, for different wavelengths; I expect to **verify, at the single-molecule level, results suggested by behavioral and ensemble *in vitro* measurements** (sub-aim 1a) such as:

- the requirement of blue light to excite the bound cofactor FAD [6] and thus initiate magnetosensing;
- the synchronous modulation of fluorescence intensity as a static magnetic field is switched on and off [19];
- the loss of magnetosensitivity in the presence of an external field oscillating with the Larmor frequency in the geofield. As one of the electrons is presumed to be essentially free of local spin interactions, effectively resonating with and tracking this particular field, the radical pair is no longer protected from the environment – hence, magnetosensitivity is scrambled, as suggested by behavioral studies with birds [20]. As the Larmor frequency is approached, I expect CRY fluorescence to become less field-dependent.

In addition, I will be able to **confirm or refute the following theoretical predictions**, which to date remain experimentally unexplored and need single-molecule techniques (sub-aim 1b):

- radical pairs are singlet-born because of spin conservation arguments [7]. Employing a commonly used model (consisting of two correlated electron spins and one nuclear spin) [21], I have already developed simulations on the quantum evolution of the radical pair; these indicate that, as the strength of an external static magnetic field is ramped up, the magnetosensitivity changes differently for radicals born in the singlet or triplet states [Fig. 4]. By measuring the magnetosensitivity as a function of the applied field strength, I will be able to estimate the distribution of initial spin states, thus quantifying the proportion of singlet-born radical pairs.
- direction-dependent magnetic field effects in anchored CRY [7]. Sensitivity to field direction is a requirement for the inclination-type magnetic compass found in birds [20], and can only be achieved if physiological CRY is at least partially anchored to a rigid cellular structure – which is not, to date, established. I will **tether single CRY**



**Fig. 3: CRY photophysics is well-understood.** **A** Absorption of light by CRY-bound FAD initiates electron transfers culminating in the formation of a radical pair. From [18]. **B** CRY is shown to primarily absorb blue light. Colors represent different delays from the photoexcitation pulse, signaling the dynamic behavior of the radical pair. From [6]. **C** (Decaying) CRY-compounds fluorescence intensity changes as a magnetic field is switched on and off. From [19].

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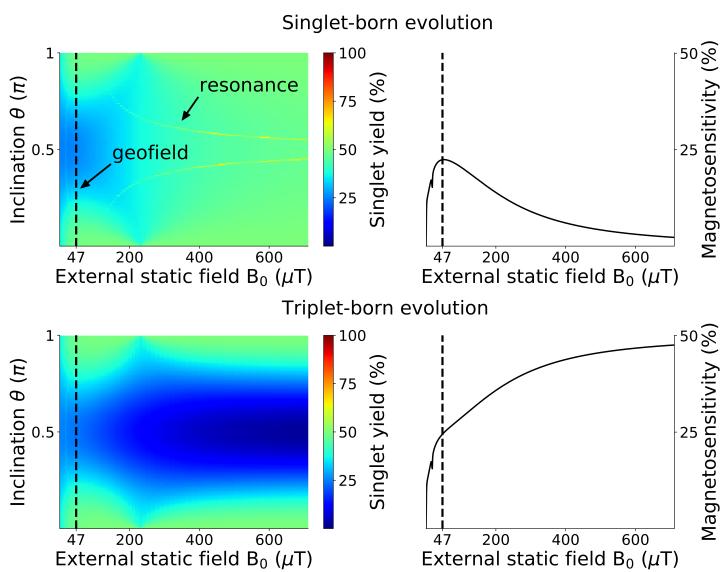
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**molecules to membrane rafts** [22], restricting their motion and thus breaking the symmetry with respect to the applied field, with aim to **compare fluorescence experiment results for anchored and tumbling single molecules**. CRY fluorescence as measured by singlet yield after radical relaxation [top left panel of Fig. 4] is expected to change as a function of field direction; moreover, a resonance may be experimentally identified. The total internal reflection fluorescence microscope is functional. Magnetic fields will be generated by miniaturized 3D coils, which I designed and are presently being built. They will be discussed in detail in aim 2.



**Fig. 4:** My simulations indicate it might be possible to experimentally differentiate singlet- from triplet-born radical pairs, and to measure direction-dependent effects. Left panels show final singlet yield after radical relaxation as a function of inclination and strength of a static magnetic field. Singlet yield changes with inclination of the applied field, which can be tracked using CRY fluorescence. Right panels show that magnetosensitivity (defined as largest difference in singlet yield over all  $\theta$ ) as a function of field strength strongly depends on the initial spin state of radical pair.

**toreception model are valid**, since my single-molecule approach will set the stage for the subsequent *in vivo* experiments (aim 2). The basic strategies developed here can be applied to the characterization of magnetic field effects in any photo-mediated chemical reaction, with single-molecule resolution. Moreover, and in the long run, adapting the total internal reflection fluorescence microscope with a pulsed light source will enable monitoring time-resolved aspects of CRY fluorescence, such as its lifetime. As another exciting extension of this aim, one can envision applying magnetic fields to control, not only observe, spin physics in CRY.

## AIM 2: TO LOCALIZE PHYSIOLOGICAL CRY EXPRESSION INSIDE FRUIT FLY LARVAE, AND IDENTIFY ITS MAGNETOSENSITIVITY SIGNATURES IN VIVO

**Rationale.** Behavioral and genetic studies of magnetosensitivity yield fascinating results which are consistent with the previously described chemical magnetoreception model. The evidence abound: birds losing their sense of direction when blue light is not present [23]; fruit flies learning how to find food by association with a magnetic field, only to ignore magnetic stimuli once CRY is knocked-out [9]; and, markedly, in a recent transgenic assay, human CRY functioning as a magnetosensor in fruit flies [24]. However exciting, these findings hint only indirectly at the underlying mechanism of magnetoreception. Thus, I propose to investigate the direct link between *in vivo* CRY functioning, in terms of its spin physics, and organismic physiology.

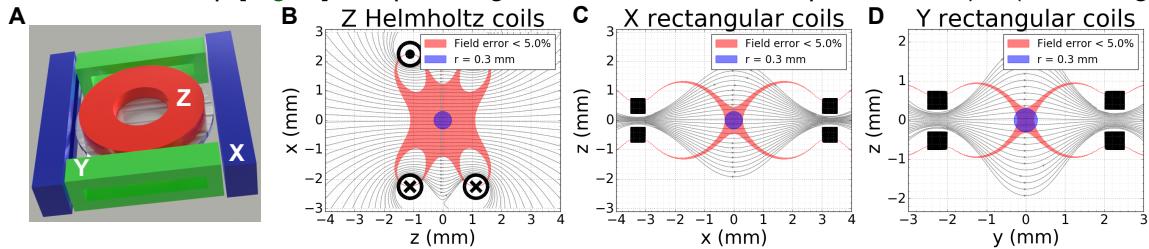
**Experimental strategy & preliminary results.** I will **combine lattice light sheet microscopy** [8], which has been developed as a low-phototoxic 3D optical tomography technique, **with synchronous electromagnetic stimuli delivered by miniaturized coils**. I am involved in the development of the second lattice light sheet microscope at Stanford University, which recently produced first images [Fig. 5]; using this setup, I will photoexcite and image a living model organism, namely a fruit fly larva. Fruit flies, extensively researched and genetically tractable, have been shown to display CRY-dependent magnetoreception in their own right [9]. The two goals of this aim are

**Limits & alternative strategies.** In the proposed experiments, it is possible that the CRY fluorescence will turn out not to be intense enough; in order to amplify the signal-to-noise and measure the magnetic field effects, which are not expected to change the fluorescence intensity by more than 1-5% [19], I will use (light and magnetic) field-modulation techniques (ex.: homodyne and heterodyne detections). Supplementary, and if necessary, I will tag CRY with a bright fluorophore that can undergo resonant energy transfer with the magnetically sensitive species (the flavin radical); in this way, the fluorophore fluorescence intensity will be a proxy for CRY magnetosensitivity. Design of a suitable protein will be done in collaboration with Prof. Lin's protein sensor engineering lab at Stanford University. Sub-aim 1 carries a low risk of failure, as the single-molecule measurements are standard, and the microscope acquisition only needs to be synchronized, via TTL pulses, with the coils' signal.

**Impact & future directions.** Accomplishing this aim will constitute the **first single-molecule experiment to investigate magnetic field effects**. In addition, it will unambiguously **inform whether primary theoretical predictions of the considered magnetoreception model are valid**, since my single-molecule approach will yield information beyond statistical averages. Finally, it will set the stage for the subsequent *in vivo* experiments (aim 2).

The basic strategies developed here can be applied to the characterization of magnetic field effects in any photo-mediated chemical reaction, with single-molecule resolution. Moreover, and in the long run, adapting the total internal reflection fluorescence microscope with a pulsed light source will enable monitoring time-resolved aspects of CRY fluorescence, such as its lifetime. As another exciting extension of this aim, one can envision applying magnetic fields to control, not only observe, spin physics in CRY.

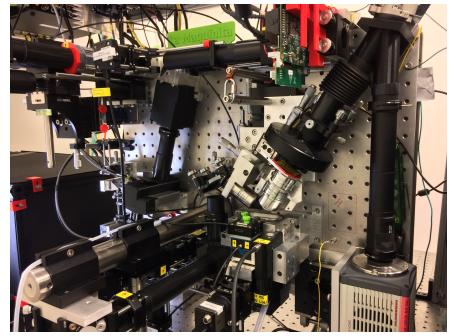
as follow. Firstly, to **establish where CRY is physiologically expressed in the larva** (sub-aim **2a**); this goal is independent of the previous aim, and will be accomplished by recording volumetric fluorescence data, with estimated resolution of  $\lesssim 250$  (400) nm in-plane (axially). I hypothesize that CRY fluorescence will be primarily observed in vision- and nervous system-related organs. This is supported by findings that magnetosensitivity is lost in cockroaches and birds with eyes covered [25, 26], and that CRY regulates the firing of fly neurons [27]. Importantly, identifying regions with higher concentration of CRY does not yield any information on its function (CRY is also notably involved in circadian clock entrainment [13]). However, since CRY is magnetosensitive, these regions do constitute ideal starting points to **search for measurable signatures of magnetic field effects (i.e. CRY fluorescence changes) *in vivo***, which is the goal of sub-aim **2b**. I will image, with high resolution, the larvae regions most strongly laden with CRY and, aligned with aim **1**, check for the synchronous modulation of CRY fluorescence in the presence of various magnetic fields. Sub-aim **2b**'s **likelihood of success is increased by the fact that I will excite the larvae with tailored magnetic fields having yielded strong magnetoresponses in the single-molecule CRY experiment of aim 1**. The magnetic fields will be provided by miniaturized coils designed not to occlude the microscope objectives (3 mm working distance), and to fit around its standard coverslip [Fig. 6]. I expect to generate uniform fields up to  $\sim 1000 \mu\text{T}$  ( $20 \times$  the geofield).



**Fig. 6: Miniaturized coils are being built.** **A** 3D coils designed to fit around a 5 mm, #1 coverslip (shown in white, below the top Z coil). Due to space constraints, only the Z coil can be designed to obey Helmholtz configuration. **B, C, D** Simulations of magnetic field lines show a large enough volume (radius  $\sim 0.3$  mm, blue circles) where experiments can be run (fields constant down to 5%, red areas).

**Limits & alternative strategies.** It is conceivable that fruit fly larvae do not naturally express a large enough quantity of CRY in order for magnetic field effects to be measured by fluorescence in our setup, even after implementation of detection lock-in techniques. If this is the case, in a first step larvae can be genetically engineered to over-express CRY [28] in collaboration with Prof. Clandinin's lab at Stanford University. Fruit fly larvae have been imaged under lattice light-sheet microscopy, so that the microscope resolution will likely be enough for sub-aim **2a**'s completion. Sub-aim **2b** carries a non-negligible risk of failure (surpassed by the thrilling possibility of it succeeding!); although *in vivo* CRY spin-relaxation times have never been measured, live flies were shown to respond (in a CRY-dependent fashion) to fields only ten times as strong as the Earth's [9], which suggest that these times will be long enough (i.e. at least  $\sim 0.07 \mu\text{s}$ ) to leave a measurable imprint on CRY's fluorescence. As an intermediate step, I will explore insect cell lines as a means to measure CRY fluorescence in a cellular environment. If necessary, though, and informed by results of aim **1**, I will consider the use of magnetic fields not only to probe, but also to control *in vivo* CRY molecules; nuclear magnetic resonance-inspired pulse sequences, with which I have extensively worked during my doctoral work, can then be applied to extend the quantum character of the radical pair. Performing these experiments at cryogenic temperatures, while beyond our current capabilities and no longer *in vivo*, would also be an enticing alternative to curb decoherence effects.

**Impact & future directions.** These experiments will **establish the first attempts at observing *in vivo* magnetosensitivity**, besides **identifying the site, within a living model organism, of physiological CRY expression**. Ultimately, though, these first *in vivo* experiments might provide insight on the actual chemical compounds used (at least by fruit flies) to sense magnetic fields. The techniques advanced with this aim, namely the combination of established volumetric light-sheet fluorescence imaging with the novel engineered application of fields, can be used, more broadly, to test the response to electromagnetic radiation of a wide range of live organisms and embryos. Furthermore, there are two natural, longer-term extensions of this aim. The first is to knock-out the CRY gene in the larvae [9] and repeat the experiments, with the objective of observing whether magnetic sensitivity is washed out as predicted by theory. The second consists in trying to monitor and influence organismic behavior via its spin physics, by the tailored excitation with magnetic fields.



**Fig. 5:** The lattice light-sheet microscope is functional, and tomographic images can be reconstructed (e.g., a TEM grid: [http://bit.ly/LLS\\_SU](http://bit.ly/LLS_SU)).

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