南方科技大学
SOUTHERN UNIVERSITY OF SCIENCE AND TECHNOLOGY

本科生毕业设计（论文）

题　　目：一个新的基于自由基对机制的鸟类地磁感应模型

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A novel biophysical model for radical-pair mechanism in birds' magnetoreception

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[ABSTRACT]: Many bird species can sense earth magnetic field and use it for navigation. Previous researches showed that FAD-Tryptophan radical pairs within cryptochrome located in outer segments of photoreceptor cells on retina might account for the magnetic orientation in night migratory birds, such as European robin. Popular hypothesis claims that radical pairs trigger an unknown downstream chemical reactions to modulate birds' night vision, but no such pathway is found till now. Here, we propose a novel biophysical theoretical model called opsin-cryptochrome competition model(OCC) to provide a direct link between the night vision and the radical pair mechanism. Comparing to all other existing model, simulation results of our model indicate a secondary amplification effect due to photon competition of opsin and cryptochrome. Experiments to verify this model are proposed.

[Keywords]: Magnetoreception; Radical pair mechanism; Opsin-cryptochrome competition model.

[摘要]：在生物导航现象中，许多种类的鸟能感受并利用地磁场来判别飞行方向。过去的研究表明，集中在感光细胞外节盘膜上的隐花色素蛋白或许是夜里迁徙的鸟类感受磁场的关键分子。在隐花色素蛋白中的黄素腺嘌呤二核苷酸和色氨酸分子能吸收一个光子产生一对自由基对，该自由基对能对不同方向的磁场做出响应。主流的猜测认为，自由基对会触发下游未知的信号通路引起视觉的形成从而“看”到磁场,但是具体的信号通路至今完全不清楚。我们提出一个全新的生物物理模型来解释夜视觉和自由基对机制之间的关系，该模型名为视蛋白-隐花色素蛋白光子竞争模型。与已有的模型相比，该模型在特定方向的磁场下可以引起二次生物放大作用，从而为自由基对机制提供一个更有力的支持。作为一个理论模型，我们提供了一些验证该模型正确性的实验思路。

[关键词]：生物地磁感应，自由基对机制，视蛋白-隐花色素蛋白光子竞争模型。

Content

1.Introduction

1.1 Migration and navigation

Many species have a long history of migration and have multisensory cues for navigation such as sun compass, star compass and earth magnetic compass[1]. For long distance migration, animals like some night migratory birds may use earth magnetic compass to navigate at night[2].

After the first discovery in 1970 that pigeons can use earth magnetic field for homing[3], many species are discovered to be able to sense earth magnetic field and use it for different purposes[4]. Three possible mechanisms for animal magnetoreception are electromagnetic induction, magnetite-based mechanism and radical pair mechanism[5].

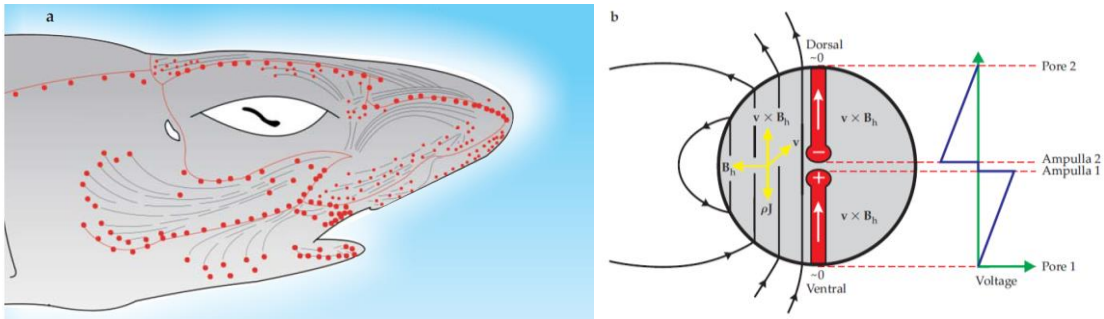

Figure-1 Electromagnetic induction mechanism in Chondrichthyes. (a) Ampullae of Lorenzini receptors(red dots) distribution in shark. **(b)** Voltage difference between two sides of a Ampullae of Lorenzini due to Electromagnetic induction, which leads to a electric signal transduction. (modified after ref.[29])

The electromagnetic induction occurs in cartilaginous fish. There is a specialized organ in Chondrichthyes called Ampullae of Lorenzini, which is a good conducting solution with a spherical structure that can accumulate electric voltage on both sides of the sphere(Figure-1). The electric difference can induce a electric signal of neurons that transduce the signal to the nervous system.

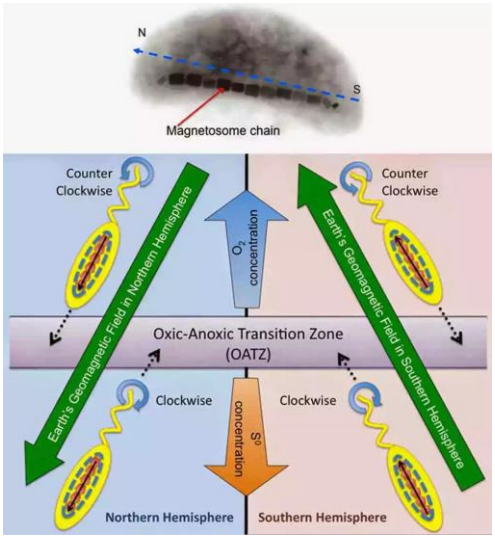

Figure-2 Magnetosome chain in magnetotactic bacteria. Magnetotactic bacteria(MTB) orientate their motion in vertical direction through magnetotaxis. The OATZ zone is preferred by MTB, which they use earth magnetic field to assist their movement towards.(modified after ref.[30])

Magnetite-based mechanism is fully verified in magnetotactic bacteria, which has a string of magnetite in micrometer size known as a magnetosome chain(Figure-2). A magnetosome chain can be orientated by earth magnetic field along the field line. The magnetic force is large enough to rotate magnetotactic bacteria, which assist the bacteria moving upwards or downwards based on the vertical component of earth magnetic field. These two mechanisms require special organs or particles in biological tissue which other animals rarely found.

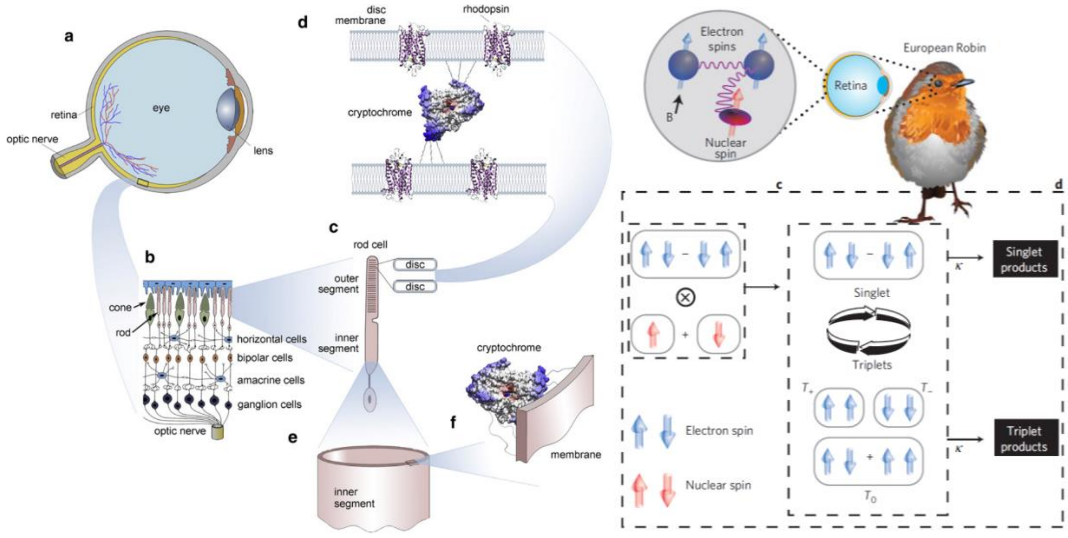

Figure-3 Schematic illustration of bird's magnetoreception of radical pair mechanism.

(A)*left* The visual structure related to magnetoreception in cryptochrome protein. a)The electric signal transduction from retina to brain via optic nerve. b)Different cell types' organization on retina. c) Rods and cones have a special arranged outer segment with a number of disk membranes. d)Predicted distribution of cryptochrome and opsin located on outer segments. e) Inner segments in photoreceptor cells. f) cryptochrome distribution in inner segments which may also account for magnetoreception.(modified after ref.[18]) **(B)***right* Radical pair mechanism in cryptochrome on birds' retina. Singlet-triplet oscillation is regulated both by internal magnetic field of nuclear spins and external earth magnetic field. The paired electron spins in a radical pair interacts with nuclear spins in vicinity, leading anisotropic hyperfine interactions which relates to the spatial anisotropy of Zeeman effect caused by earth magnetic field.(modified after ref.[31])

We focus on the radical pair mechanism among the three mechanisms for it has increasing evidences for magnetoreception in night migratory birds such as European robin(Figure-3)[6]. Evidences are listed below. Recent finding shows a neural connection between night vision and magnetic sensing. Bilateral lesion of cluster N as a part of vision brain area in European robin results in its magnetic disorientation[2]. The flavin adenine dinucleotide (FAD) and tryptophan triad within a cryptochrome protein can form a radical pair induced by a photon, which form the basis of radical pair mechanism. The cry4 protein, a member of cryptochrome family, is found recently located on the outer segment in cones in birds' retina(Figure-4)[7] and is considered to be a candidate to response to earth magnetic field. Different wavelength of incident light and radiofrequency electromagnetic field can disrupt magnetic orientation of European robin[8-12,17]. Moreover, European robin derives their north direction by the smaller angle between the magnetic field vector and gravity vector rather than the polarity of earth magnetic field[6,13]. It shows that the magnetic compass is actually an inclination compass instead of a polarity compass, which can be explained by the radical pair mechanism. Further, the <5 degree precision of birds' magnetic compass can only be explained by the radical mechanism[14]. These behavioral and neural experiments provide indirect supports for the radical pair mechanism.

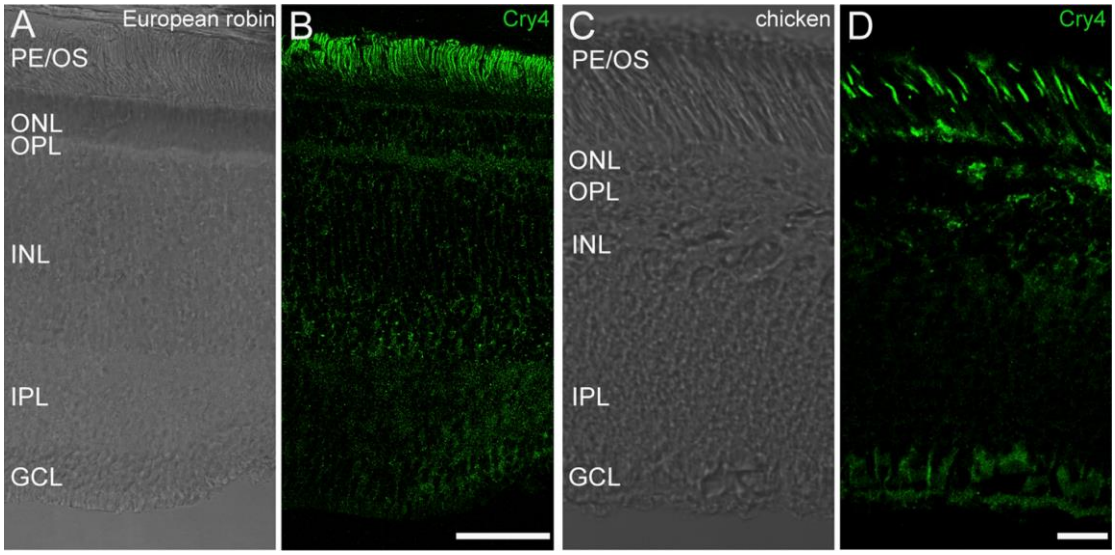

Figure-4 Cry4 is expressed in the outer segments in double cones and long wavelength single cones in the Retina of European Robin and Chicken. Bright field image **(A)(C)** and immunostaining **(B)(D)** of cry4 protein. (modified after ref.[7])

1.2 The radical pair mechanism

Radical pair mechanism was first proposed by Klaus Schulten, based on a quantum mechanical effects of radical pairs under external magnetic field[16]. As the only one candidate protein for light-induced radical pair formation, cryptochrome can absorb one photon with wavelength ranging from 400-565nm to generate a FAD-TrpH radical pair[17].

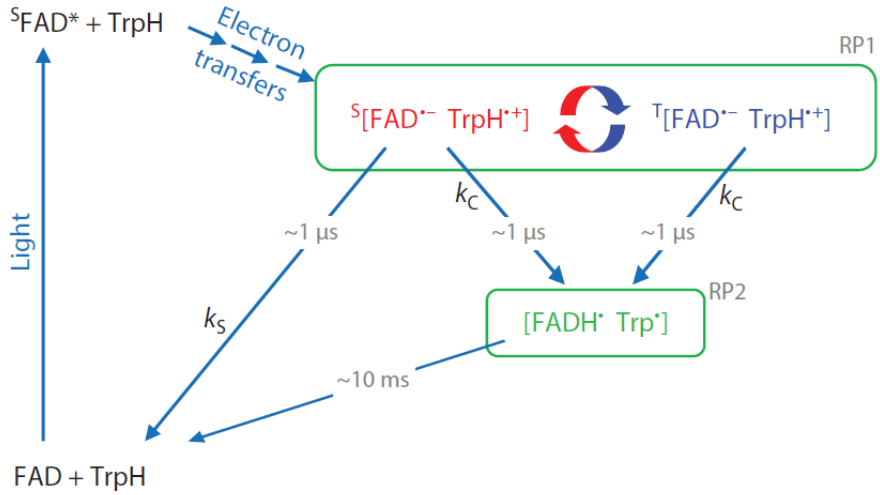

Figure-5 A FAD-TrpH radical pair formation and reactions in cryptochrome. After excited by an incident photon, FAD molecule is in a excited singlet state and electron transfer from

tryptophan to FAD to form a transition state in singlet state. Due to the hyperfine interaction, a singlet-triplet interconversion occurs regardless of external magnetic field. The singlet state rapidly recovers to ground state whereas triplet state react into FADH-Trp radical pair via a change of protonation. The FADH-Trp radical pair recovers slowly into ground state. (modified after ref.[1])

The radical pair mechanism are described below(Figure-5)[6]. Firstly, a photon hits on FAD molecule and cause an electron transfer along the triad tryptophan onto FAD molecule forming a singlet transition stat. The singlet state FAD-TrpH can be recovered to the ground state whereas the triplet state FAD-TrpH reacts into a FADH-Trp radical pair by a change in the protonation state. The lifetime of FADH-Trp radicals (~10ms) are much longer than FAD-TrpH radicals(~1us). So it causes a huge difference in lifetime of the products led by different states of radical pairs. Comparing to short life time, long lifetime of radical pair maintain an excited state inhibiting another photon absorption of FAD molecule.

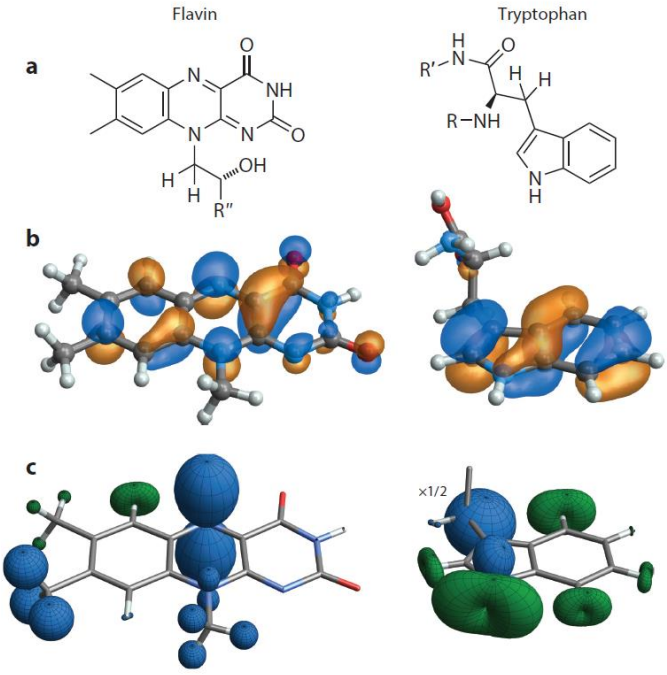

Figure-6 Molecular orbitals and hyperfine interactions in flavin and tryptophan radicals. On the left side it is flavin molecule while on the right side, it is tryptophan molecule. **(a)** Chemical structure. **(b)** Molecular orbitals. **(c)** Hyperfine interaction of the nuclear spin and electron spin in a FAD-Trp radical pair. (modified after ref. [1])

Secondly, the singlet-triplet oscillation occurs once singlet transition state is generated and it is caused by the hyperfine interaction and Zeeman effect on free electrons of radicals[6]. Hyperfine effect is due to the interaction between the electron spins and the nucleus spins in vicinity whereas Zeeman effect is caused by the external magnetic field. As a result of the anisotropic hyperfine effect on FAD molecule(Figure-6), unpair electrons are more likely to distribute in one specific direction 'z' than the other two directions(Figure-7A) which leads to a variation of singlet-triplet oscillation. As long as the spin decoherence time is longer than the life time of FAD-TrpH radical pairs, the magnetic compass remains functional. The principle of the radical pair mechanism is formulated in Appendix A.

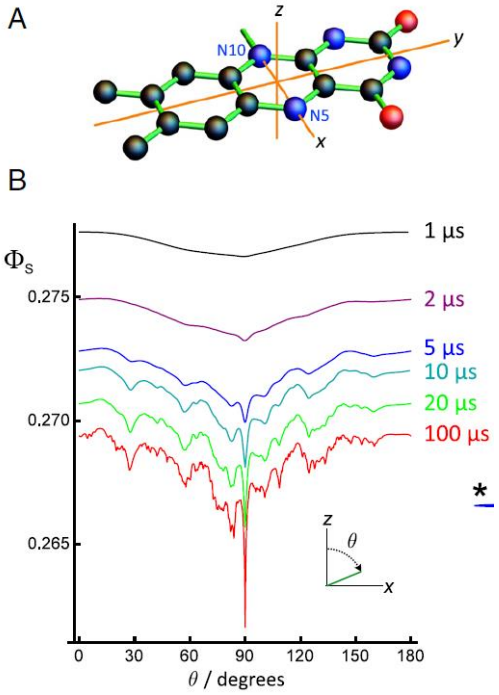

Figure-7 Simulation of the quantum effect of a FAD-Trp radical pair under external magnetic field. (A) The axis system on the flavin ring system. **(B)** Reaction yields of singlet radical pair [FAD•− TrpH•+]. θ is the direction of the external magnetic field in reference to the zx plane of the flavin. (modified after ref.[14])

Sensing the magnetic field in radical pairs is the first amplification effect in biological system. But a secondary biological amplification is still needed to convert a physical detectable signal into a biological detectable signal. The conventional hypothesis it that different lifetimes of radical pairs may trigger a noncanonical visual

pathway that transforms chemical signals into a membrane electric signal to modulate bird's night vision[18]. Unfortunately, no such biological pathway is found till now.

1.3 Visual system in vertebrate

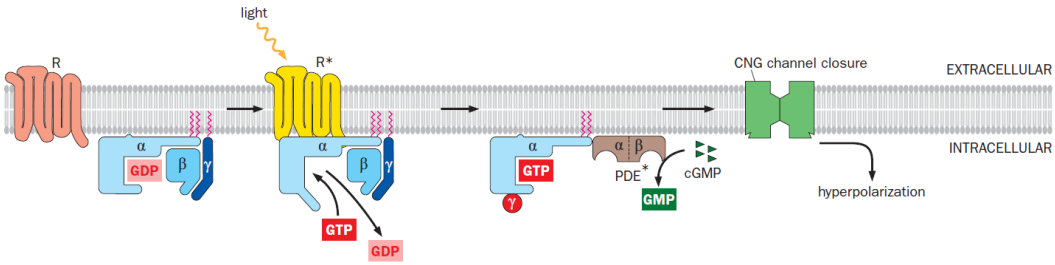

Figure-8 Phototransduction cascade. R* represents activated rhodopsin protein on the disk membrane of outer segment. After absorption of a photon, a GPCR protein release its β,γ subunits via GTP hydrolysis. The α subunit of GPCR will activate PDE(phosphodiesterase) to convert the cyclic GMP into GMP. Decrease of cGMP leads to the closure of CNG channel generating a hyperpolarization on the membrane potential which is a electric signal of transfer visual information of photoreceptor cells. (modified after ref.[19])

Visual system in the vertebrate is quite known in the aspect of molecular pathways. Rhodopsin is the major photoreceptor in the light perception and initiates visual phototransduction(Figure-8)[19].

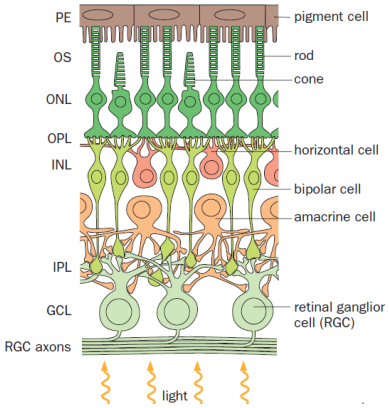

Figure-9 Organization of the retina. Photons input from the bottom. PE, pigment epithelium; OS, photoreceptor outer segments; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. (modified after ref.[19])

A specialized structure called outer segment in the rod cell have parallel disk membranes to locate opsins for maximizing light absorption(Figure-9,10[22]). A rod cell can be activated by a few photons under dark condition[6], which is a single photon

detector with a high sensitivity[20,21]. Night migratory birds mainly utilize rod cells for night vision and cone cell for dim light situation. To emphasize, cryptochrome protein such as cry4 expressed in birds' outer segment of cone cells may be a potential competitor together with opsins for light absorption(Figure-4).

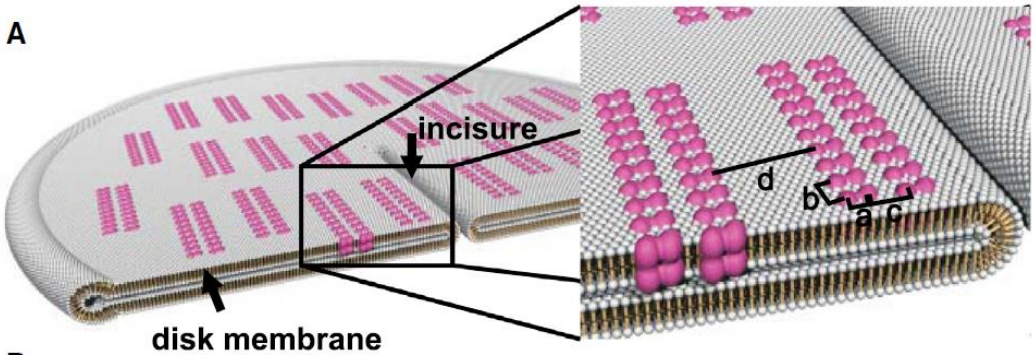

Figure-10 Model of rhodopsin distribution on the disk membrane. The number of rhodopsin on one disk membrane is about 2100. According to the tomography model, a=4nm; b=5nm; c=5nm; d=15nm on average. (modified after ref.[22])

For light intensity detection, animal eyes performed a complicated mechanism which is not fully understood till now. In 1820s, a German physiologist Ernst Weber proposed a light intensity response law in physiological level[19]. The Weber's Law claims that the minimal variation of intensity over intensity strength that can be sensed by human eyes is a constant called increasement threshold also known as Weber fraction for human eyes[15]. If the actual light stimulation is under this threshold, one could not distinguish the difference before and after the stimulus. So, light perception is not simply correlated with the photon numbers but rather the difference of incident photon relative to its background intensity in vicinity or at early moment. Although a more complicated relation with different range of light intensity is found, the Weber-Fechner law is still a good approximation under a mesopic condition. In birds eye, there is lack of study of its increasement threshold under dim light intensity. So we use the Weber fraction of human eye as a comparable parameter in our model since night migratory birds are more sensitive to dim light.

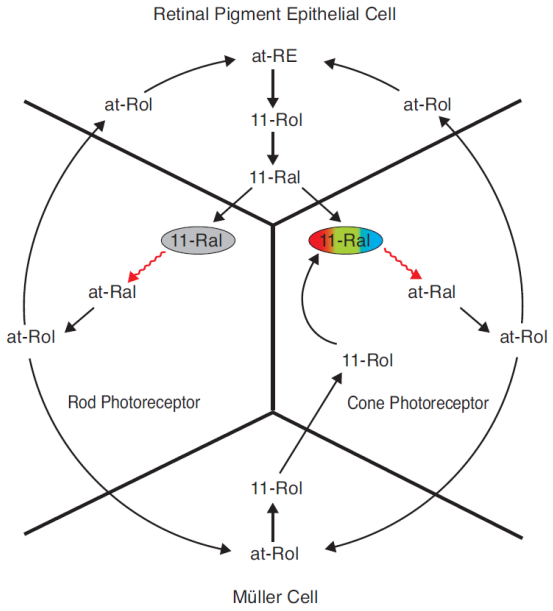

Figure-11 Visual cycle of rods and cones. In both rods and cones, after phototransduction, cis-retinal is converted into trans-retinal and is dissembled off a cryptochrome. Trans-retinal reacts into trans-retinol which is delivered into RPE(retinal pigment epithelial cell) to convert back into cis-retinal molecules. The whole cycle is call a rod visual cycle. (modified after ref.[28])

The molecular pathway of a rod visual cycle as shown in Figure-11, is a dynamic biological pathway for formation and consumption of cis-retinal[28]. Retinal is a chromophore in rhodopsin. After absorbing a photon, it is converted into trans-retinal which can induce a conformational change of rhodopsin to have a downstream phototransduction. The trans-retinal cannot absorb photons anymore, so trans-retinal is removed by other proteins and transported to retinal pigment epithelial cells in order to convert the chromophore back to cis-retinal conformation. After conversion, the cis-retinal is transported back to outer segment of rod cells and reassemble onto opsin to become functional rhodopsin. A full rod cell cycle from trans-retinal disassembly to cis-retinal reassembly required about 40 minutes, whereas cone cells only require 2-3 minutes to accomplish one cycle[28].

3.Biophysical model

We propose a new biophysical model that can directly explain how a magnetic sensor regulates visual formation. Based on opsin cryptochrome competition model, cryptochrome protein does not account for the phototransduction for visual formation,

but it has capability to compete with rhodopsin to absorb photons which lead to a change of light perception pattern in rods or cones. Photoreceptor cells are sensitive to light intensity on which the competition model relies. Here are the mechanism of our model:

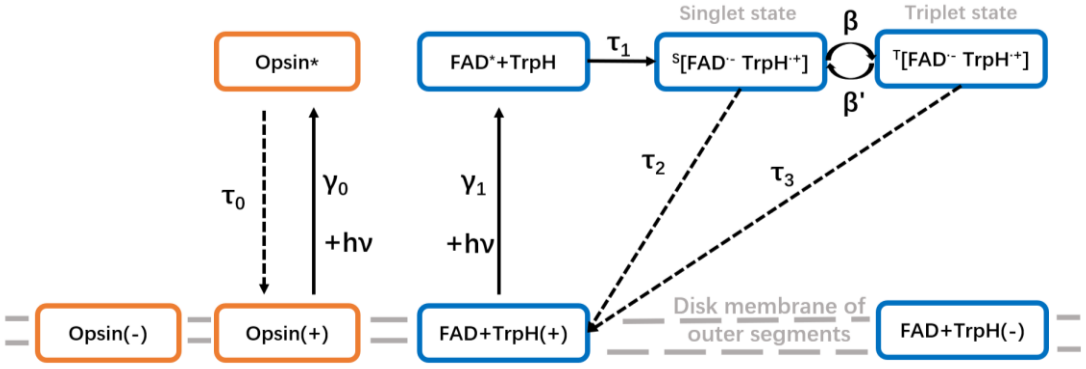

Figure-12 Opsin-Cryptochrome Competition Model. FAD and TrpH molecule are located in the cryptochrome protein while cis-retinal is located in rhodopsin. These two molecules undergo a photon competition with a shared range of light wavelength.

As shown in Figure-12, we introduce two key components in our model. One is the rod or cone photoreceptor cycle contributing to bird's vision represented by opsin(orange part). The other is FAD and tryptophan molecules(blue part) representing a cryptochrome light absorption cycle that competes with opsin. Opsin and cryptochrome are considered to be distributed on the disk membranes of outer segments in rods or cones.

Different symbols represent different states of molecules: (-) represents the ground state of molecules that have no light stimulation; (+) represents the ground state of a molecule hit by one photon; (*) represents the excitation state of a molecule after photon absorption; (s) and (t) represent the singlet and triplet state of a molecule. γ and β are first-order reaction rate constants while τ is lifetime defined as a reciprocal of the rate constant of the reaction.

$$N_{op}^{(+)} + N_{op}^{*} + N_{op}^{(-)} = C_1 \tag{1}$$

$$\frac{d(N_{op}^{(+)} + N_{op}^{(-)})}{dt} = -\gamma_0 N_{op}^{(+)} + \frac{1}{\tau_0} N_{op}^{*} \tag{2}$$

$$\frac{dN_{op}^{*}}{dt} = \gamma_0 N_{op}^{(+)} - \frac{1}{\tau_0} N_{op}^{*} \tag{3}$$

$$N_{FAD}^{(+)} + N_{FAD}^{*} + N_{FAD}^{Singlet} + N_{FAD}^{Triplet} + N_{FAD}^{(-)} = C_2 \tag{4}$$

$$\frac{d(N_{FAD}^{(+)} + N_{FAD}^{(-)})}{dt} = -\gamma_1 N_{FAD}^{(+)} + \frac{1}{\tau_2} N_{FAD}^{Singlet} + \frac{1}{\tau_3} N_{FAD}^{Triplet} \tag{5}$$

$$\frac{dN_{FAD}^{(*)}}{dt} = \gamma_1 N_{FAD}^{(+)} - \frac{1}{\tau_1} N_{FAD}^{*} \tag{6}$$

$$\frac{dN_{FAD}^{Singlet}}{dt} = \frac{1}{\tau_1} N_{FAD}^{*} - \frac{1}{\tau_2} N_{FAD}^{Singlet} - \beta N_{FAD}^{Singlet} + \beta' N_{FAD}^{Triplet} \tag{7}$$

$$\frac{dN_{FAD}^{Triplet}}{dt} = \beta N_{FAD}^{Singlet} - \beta' N_{FAD}^{Triplet} - \frac{1}{\tau_3} N_{FAD}^{Triplet} \tag{8}$$

$$N_{op}^{(+)} + N_{FAD}^{(+)} = N_{photon} \tag{9}$$

$$R_{opsin} = \frac{N_{op}^{(+)}}{N_{photon}} \tag{10}$$

According to our model, we build up a set of linear differential equations with some assumptions. Equations (1)-(3) are the dynamics of rhodopsin where C_1 is the total number of opsins which is a constant. Equations (4)-(8) are the dynamics of FAD-TrpH molecules where C_2 is the total number of cryptochrome which is a constant for each cryptochrome have one pair of FAD-TrpH molecule. We assume that no photon can escape from the absorption by opsin or cryptochrome. Therefore, the sum of two proteins in (+) state always equals to the constant number of incident photons shown in equation (9). The ratio of opsin(+) and incident photon in equation(10) is an index reflecting the relative percentage of photons that are absorbed by opsin. If a sufficient difference of the ratio is made under various direction of earth magnetic field, birds are very likely to see the light intensity change due to the photon competition by opsin and cryptochrome.

With a long time evolution with constant incident photons, the linear system tends to be in a steady equilibrium where the concentration molecules in different states remains unchanged. So the left side of the Equation(2)(3)(5)-(8) can be set as zero. We will get a time-independent stationary solution of the equations whose details are discussed in Results.

3.Results

3.1 A stationary solution of equations

From the equation (1)-(3), we get equation(11)(13). From equation (4)-(8), we get equation(12)(14).Then we get a quadratic equation(15) from equation(9). Two solutions for the quadratic equation can be obtained and we take the solution with positive sign to obtain equation(16) which fits the physical meaning of the model.

In the solution, R_{opsin} is the competition ability of opsins against cryptochrome. It is a function of γ, β and τ and involves the C_1, C_2 and N_{photon} constants.

$$N_{op}^{(-)} + B * N_{op}^{(+)} = C_1 \tag{11}$$

$$N_{FAD}^{(-)} + A * N_{FAD}^{(+)} = C_2 \tag{12}$$

$$B = \tau_0\gamma_0 + 1 \tag{13}$$

$$A = 1 + \gamma_1(\tau_1 + \frac{1}{\frac{\beta'}{\tau_2\beta} + \frac{1}{\tau_2\tau_3\beta} + \frac{1}{\tau_3}} + \frac{1}{\frac{1}{\tau_2} + \frac{\beta}{\tau_3\beta'+1}}) \tag{14}$$

$$(A-B)N_{op}^{(+)^2} + (C_1 + C_2 - N_{photon}(A-B))N_{op}^{(+)} - N_{photon}C_1 = 0 \tag{15}$$

$$R_{opsin} = \frac{-(C_1 + C_2 - N_{photon}(A-B)) + \sqrt{(C_1 + C_2 - N_{photon}(A-B))^2 + 4N_{photon}C_1(A-B)}}{2N_{photon}(A-B)} \tag{16}$$

3.2 Parameter initiation

To make it simple, we set the number of opsin is equal to the number of cryptochrome (C_1=C_2). The actual number of opsin in the outer segment of one photoreceptor cell can be calculated by cryo-EM tomography(Figure-10)[22], which is approximately about thousand proteins per disk membrane. It is roughly thousand disk membranes in the outer segment of rods[28]. So the total number of proteins is around a million. Under the dim light or moon light, at least 10^3 photons per second is required to stimulate the human cone vision and few photons per second for human rod vision. So the ratio of incident photon to number of proteins are about 10^{-3} for cones and 10^{-5} We initialize C_1, C_2 and N_{photon} in the ratio of 1:1:10^{-3}. Since the light perception pattern in rod cells is more unclear than cone cells, so we simulate only the situation of cone cells.

As for γ_0 and γ_1, which refer to the light absorption rate constant of opsin and

cryptochrome respectively, they both have ultrafast reaction rates where we set them in the same order of magnitude($\gamma_0=\gamma_1=10^{15}$/s). Electron transfer from tryptophan to FAD molecule also has a rapid speed and therefore we set τ_1=1ns. According to previous study in the lifetime of single and triplet product[14], FAD-TrpH radical pair is estimated to have a lifetime about 1us. So we set the lifetime τ_2=1us whereas τ_3=10ms for triplet product has to return to ground state only after a change of protonation state which takes time[6].

We then come to deal with τ_0 and β which are difficult parameters to be estimated. For a single rhodopsin molecule, τ_0 is 40 minutes for rods and 2-3 minutes for cones due to the recovery cycle of cis-retinal[28], which doesn't fit the actual visionary cycle where the frame rate of human eyes is about 30-60Hz. The reason why the lifetime of a single rhodopsin cannot represent the actual situation is that light perception in photoreceptor cells is a more complicated situation for example the light contrast is not due to the total incident photon number but rather the relative difference in photon number in vicinity. Another reason is that the single molecular lifetime correlates to a whole rod visual cycle without considering the initial concentration. For cis-retinal supply, photoreceptor cells continuously transport an amount of trans-retinol molecules to retinal pigment epithelial cells but also import a large amount of cis-retinal into outer segment to supply the function of opsins[28]. The dynamics of this visual cycle cannot be analyzed by an single cis-retinal recovery pathway. So we use a macroscopic index that is the framerates of a bird's eye to define τ_0=5ms approximately.

To estimate β and β', one should understand the singlet-triplet interconversion pattern. The oscillation between singlet state and triplet state of electron spins in radical pairs are consequences of isotropic and anisotropic hyperfine effect of nuclear spins of the radical. The oscillation frequency of hyperfine effect and Zeeman effect are 10^{15}Hz and 10^{7}Hz respectively. The lifetime of the radical pair is much larger than the periods of oscillations resulting in an average concentration of singlet and triplet interconversion. We derive the parameter β from a computational simulation by the group of Peter Hore[14] whereas β'=0 due to no net conversion from triplet state to singlet state during a sufficient long time. Based on Figure-7, we can use equation

$\beta=\Delta(\Phi_s)/\Delta(t)$ to get the different values under different angle θ, which is the angle between earth magnetic field and direction 'z' as shown in Figure-7(A).

However, estimation of τ_0 and β needs more experimental measurements of the retinal dynamics and singlet-triplet interconversion. These two parameters will be further discussed in Discussion.

3.3 Computational simulation

Firstly, we derived the β coefficient from the simulation result (τ_2=1us) of the quantum needle[14]. As shown in Figure-13a, the fractional yield of singlet state radical pair change slowly with angle. According to the relationship $\beta=\Delta(\Phi_T)/\Delta(t)$, we can obtain the relationship between β and angle θ in Figure-13b.

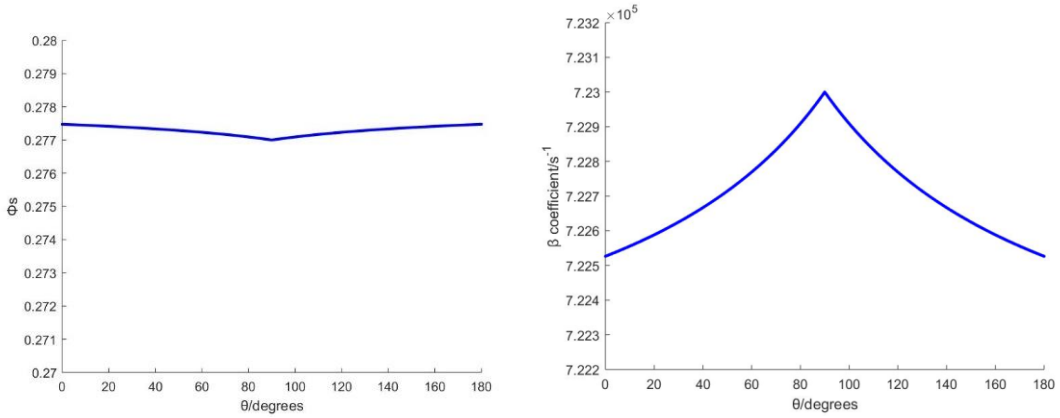

Figure-13 Fractional yield of singlet state and derived β coefficient under earth magnetic field with various angles. (a) *left:* Fractional yeild of singlet product with various θ derived from Figure-7B. **(b)***right:* β coefficient derived from (a) using the relation $\beta=\Delta(1-\Phi_s)/\Delta(t)$.

From Figure-13a, the fractional yield of singlet product has a little variation between 0° and 90° which represent the angle of the earth magnetic field and the 'z' direction of FAD molecule. Due to the same orientation of FAD molecules on disk membrane, the angle changes the same difference as a bird rotate its head. Head orientation leads to the change of the angle between the FAD molecules and earth magnetic field. The orientation of FAD molecules results in different visual patterns when a bird see from different angle. This rotation-vision conversion relation stores its information via β coefficient which is derived from Figure-13a and is a key estimated parameter used in our biophysical model.

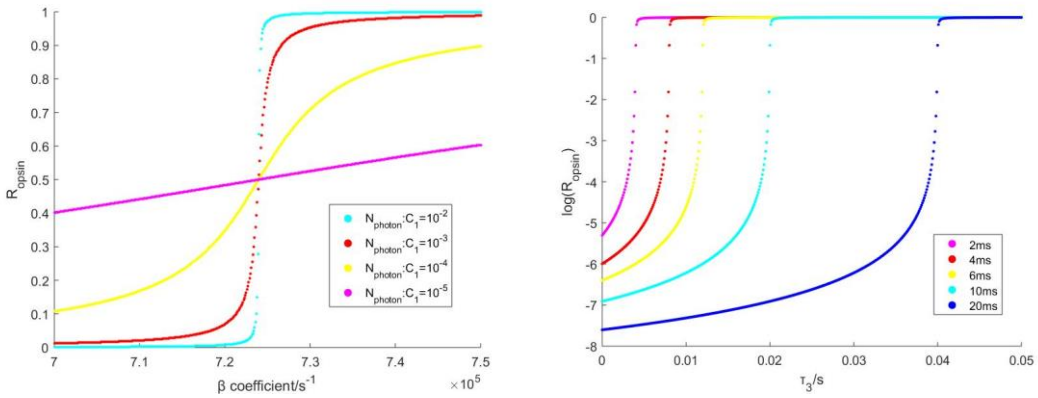

Figure-14 Photon competition of opsin and cryptochrome. (a)*left*: Photon absorption ratio with various β parameter under different incident photon numbers(N_p). The R_{opsin} change more steeply when incident photon increases ranging from few photons to thousands photons. **(b)***right:* Logarithm of photon absorption ratio with change of τ_3 parameter under different opsin recovery time(τ_2). Under the condition that β is big enough to make R_{opsin} up to 100%, when opsin recovery time is short below 4ms, the amplification effect is huge to change R_{opsin} from 0 to 1.

Secondly, based on the stationary solution of differential equations, we can get the relationship between ratio of photon absorption by opsin and β coefficient. Figure-14 shows that the ratio steeply changed from 0 to 1 with a small range of β, which indicates an amplification effect of the competition model. When the ratio is near 0, almost no photon is absorbed by opsins whereas almost all photons are absorbed by opsins when the ratio is near 1. The steep region can be easily understood through equation(16). In equation(16), the denominator has a (A-B) term where the result can be changed dramatically when A=B. A and B are two parameters correlating to opsin-related visual pathway and cryptochrome-related reaction respectively. When singlet-triplet interconversion changes with different orientation of earth magnetic field, the fractional yield of singlet and triplet product also alter where β is changed in coefficient B. So the coefficient B is changed to approach to A where the magnetic field effect will amplify by the steep response to new β.

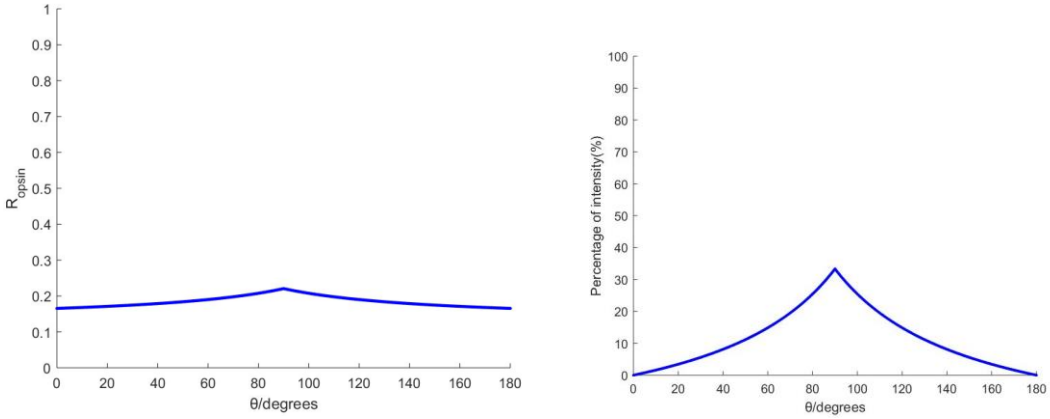

Figure-15 Photon absorption ratio and relative intensity change due to earth magnetic compass. (a)*left:* Photon absorption ratio with change of θ. **(b)***right:* Light intensity difference over basal intensity at θ=0 change with various θ. Parameter setting: τ_0=4.2ms; τ_1=1ns; τ_2=1us; τ_3=10ms; β'=0; C_1:C_2:N_{photon}=1:1:10^{-3}; γ_0=γ_1=10^9/s. β is calculated in term of relationship in Figure-13b.

Thirdly, we can simply combine the first and the second simulations to get the actual photon absorption ratio with different angles as shown in Figure-15a. Based on the light intensity response of photoreceptor cells, the increment threshold is around 14% and 1.5% for rods and cones respectively. From the light intensity change relative to the peripheral light intensity in reference to =0°(Figure-15B), the Weber fraction at the center can be up to 30% (θ=90°). That indicates that a bird can distinguish the variation of light intensity through a head rotation of about 30° from the center(θ=90°). Furthermore, it is a simulated evidence to support our hypothesis that birds can "see" the magnetic field directly under the photon competition between opsins and cryptochrome.

4.Methods

All the figures from Results are simulated by MATLAB software. Source codes can be obtained in github (https://github.com/LokyWei/Biophysical-model).

5.Discussion

5.1 A comprehensive review on radical pair mechanism

After the first appearance of radical pair reaction used in explaining the

magnetoreception, scientists have been stuck for nearly twenty years in connecting the physical and biological mechanism in radical pair mechanism. The quantum effect of an unpaired electron can be the most potential candidates accounting both for detection of earth magnetic field and for utilization by some kind of animals such as pigeons, robins, salamanders, sea turtles and etc.[23] The major reason why birds such as European robins and home pigeons are model organisms is that they utilize earth magnetic field for navigation and night migration. Most species can response to earth magnetic field but lack of a clear behavioral purpose which adds difficulties for study. This is also the reason that traditional model organisms like *Drosophila* and zebra fish are not ideal model animals for studying magnetoreception although they are reported to have capability to sense earth magnetic field[24,25].

As for detection of earth magnetic field, singlet-triplet interconversion can be an effective mechanism to amplify the earth magnetic signal via spin dynamics. Other mechanism such as electromagnetic induction can be only achieved in cartilaginous fish[5] whereas magnetite-based mechanism only accounts for magnetoreception in magnetotactic bacteria and almost no evidence supports its significance in animal magnetoreception. All the mechanisms are facing the most important problem whether it is sufficient to detect earth magnetic field, which is indeed very week. Models based on classical mechanics almost fail in animal magnetoreception. It is the first motivation for us to try thinking in a quantum mechanical way.

With recent development in behavioral biology and neurophysiology, scientists found out more evidences to support that magnetoreception occurs on birds' retina under the controlled experiments such as stimulation of different light wavelength, damage of visual related brain region and intensity change of incident photons. The radical pair mechanism is the only one hypothesis that is correlated with light stimulation. In order to sense earth magnetic field, molecules with structurally organized spatial orientation must be considered firstly. Rods and cones both have specialized structures such as outer segments fit this requirement. And it is known that the different light wavelength can alter the sensitivity of earth magnetic field. So molecules that can response to visible light in specific range of wavelength may also

be a potential candidate. Since cryptochrome expressed in retina is the only protein candidate in vertebrates that can each time absorb a photon and then produce a long-lived radical pair[1]. Therefore, cryptochrome in photoreceptor cells are proposed to be a magnetic sensor.

But yet, a direct link between the molecular mechanism in biology and the potential magnetic sensor is still unknown to us. A mainstream hypothesis is that cryptochrome proteins can trigger a downstream signal transduction to modulate birds vision. But till now, downstream signaling pathway is still fully unknown. There are several reasons: firstly, the C-terminal of birds' cryptochrome is important for chemical activity of FAD molecules and it is a flexible region loosely wrapped[26]; Secondly, cryptochrome is a multifunctional protein that is a key component of biological rhythm[26]. It involves in a regulatory pathway in biological rhythm whereas magnetoreception will be a secondary effect of this protein. If a downstream signaling pathway exists and differs from the canonical visual pathway, a secondary biological amplification will be vital for radical pair mechanism to achieve magnetoreception.

That is why the photon competition model is proposed. The model connects the biological mechanism together with the magnetic sensor in a direct way. The secondary amplification effect is due to the photon competition of opsin and cryptochrome. The competition leads to a dramatic change in light absorption between opsin and cryptochrome, which causes a visual contrast under various light intensity. Our novel model better fits the situation at starry night or under dim light such as foggy days. During day light, the photon is sufficient for both opsin and cryptochrome, so the competition might not occur. Many behavioral experiments on birds and other animals are under the condition of overcast or night[1,27]. Without other sensory cues such as sun and star location, specific odors and landmarks, birds are forced to use magnetic compass for navigation. During day time, lots of other cues can be used for navigation and can compensate with each other. It still lacks of decisive experiment to show whether the magnetic compass can fully function in migratory birds during day time.

5.2 Limitations

Our model has several estimated parameters that may lead to approximations to the real situation. In spite of some limitations, the philosophical idea of the model does not change and it is more important to perform experiment under instructions of theoretical predictions.

Due to the complicated situation of biological reactions, most parameters we use in the model has no solid experimental measurements, rather, it is an empirical estimation such as a chemical reaction with purified substances in test tubes. During the coherence state of radical pair, the lifetime of the singlet and triplet state are always treated simply as the same around 1us without experimental confirmation. The approximated rate constant β need to be calculated by quantum transition state theory where here we only simply treated as an classical rate constant in order to keep the equation in a linear form with a stationary solution. The roughest estimation is the recovery time of opsin(τ_0). Although the visual cycle is known to us, the dynamics and kinetics of cis-retinal and trans-retinal is complicated in living cells. The dynamics of chromophores involves the assembly rate of retinal molecule onto opsins, the concentration of retinal molecules in outer segments, diffusion velocity of retinal molecules and removal rate of retinal molecule from rhodopsin. Each of those physical quantities can affect the recovery time of rhodopsin. In order to model this process, a stationary solution of a set of linear differential equations is good to be dealt with the complicated situations to reveal the key properties of this model.

One important question of radical pair mechanism is whether the magnetic sensor works in rod cell or in cone cell or both. No experiment has shown any preferences yet. So in principle, both photoreceptor cells are possible candidate and need to be carefully identified.

5.3 Experimental confirmation

From result, we know photon number is vital for visual formation of earth magnetic field. So there exists a photon threshold that can alter the capability of magnetic compass. Controlled experiment of incident light intensity on magnetic compass will help prove or disprove our theoretical model. Besides, the

magnetoreception is directly correlated to light perception in rods or cones which means that birds can detect the small intensity change of the visual background due to the earth magnetic field. Background intensity may increase than decrease changing with visual angle. Background disruptions can be performed in the experiment. We can design an apparatus that can decrease than increase the background intensity changing with the same visual angle. Such apparatus need to detect the direction of the earth magnetic field and automatically adjust the direction of the compensation light within the range of the absorption spectrum of FAD molecules.. The sum effect of the magnetoreception and the compensation will be balanced. So no background difference can be detected or the successful light disruption causes magnetic disorientation.

5.4 Summary

Different mechanisms contributes to explain the magnetoreception across different species. Different species seems to have different mechanisms to sense earth magnetic field. And they may utilize it with various known and unknown purpose. Magnetoreception may be a side effect which acquired accidentally in some species during evolution. Animals like bird have multisensory cues to assist their navigation. So it is a flexible choice for most animals that can use or abandon the capability of magnetoreception. Opsin cryptochrome competition model can in principle contribute to a secondary biological amplification after the first physical amplification by the radical pair mechanism for magnetoreception.

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Appendix

Appendix A – Principle of the radical pair mechanism

Here, we only discuss a simple case of anisotropic hyperfine interaction of nuclear spins and Zeeman effect on electron spins in the FAD-Trp radical pair mechanism. The fractional yield of singlet and triplet state product is $\Phi_S=1-\Phi_T$ is an integral of the real part of T(t) which is the singlet fraction at arbitrary time t.

$$\phi_T = k_T \int_0^\infty T(t)dt \tag{17}$$

$$T(t) = Tr[Q^T \rho(t)] \tag{18}$$

Q^T is the projection operator of triplet state while ρ(t) is the density matrix of the radical pair at arbitrary time. The triplet state fraction is a trace operation of the density matrix projected on the triplet state product.

$$\rho(t) = \frac{1}{N} e^{-\frac{iHt}{\hbar}} \rho(0) e^{\frac{iHt}{\hbar}} \tag{19}$$

Assume there is only singlet product at time 0, where $\rho(0)=Q^S e^{-kt}$, here to make it simple, we let $k=k_S=k_T$. N is the number of nuclear spin.

The Hamiltonian for two electron spins are H_1 and H_2 respectively. $\vec{B}$ is the magnetic field vector with a specific direction.

$$H = H_1(\vec{B}) + H_2(\vec{B}) \tag{20}$$

$$H_j = g\mu_B \vec{S_j} \cdot (\vec{B} + A_j \vec{I_j}) \tag{21}$$

S_j is the electron spin operator whereas I_j is the nuclear spin operator correlated with the nuclear spin in vicinity. A_j is the anisotropic coefficient of the nuclear spin which is the key term to generate spatial anisotropy of under various directions of external magnetic field.

$$T(t) = \phi_S = 1 - Tr[Q^T \frac{1}{N} e^{-\frac{iHt}{\hbar}} Q^S e^{-kt} e^{\frac{iHt}{\hbar}}] \tag{22}$$

$$= \frac{1}{N} Tr[Q^T e^{-\frac{iHt}{\hbar}} Q^S e^{\frac{iHt}{\hbar}} e^{-kt}]$$
$$= \frac{1}{N} \sum_{mn} \langle m| [Q^T |n\rangle \langle n| e^{-\frac{iHt}{\hbar}} Q^S e^{\frac{iHt}{\hbar}} e^{-kt}] |m\rangle$$
$$= \frac{1}{N} \sum_{mn} \langle m| Q^T |n\rangle e^{-\frac{iHt}{\hbar}} \langle n| Q^S |m\rangle e^{\frac{iHt}{\hbar}} e^{-kt}$$

$$= \frac{1}{N} \sum_{mn} \langle m| Q^T |n\rangle e^{-i\omega_n t} \langle n| Q^S |m\rangle e^{i\omega_m t} e^{-kt} \tag{23}$$

We can let:

$$\langle m| Q^T |n\rangle = Q^T_{mn}, \langle n| Q^S |m\rangle = Q^S_{nm}$$

$$\phi_S = 1 - \phi_T = 1 - k \int_0^\infty \frac{1}{N} \sum_{mn} Q^T_{mn} e^{-i\omega_n t} Q^S_{nm} e^{i\omega_m t} e^{-kt} dt \tag{24}$$

$$= 1 - \frac{k}{N} \sum_{mn} Q^T_{mn} Q^S_{nm} \int_0^\infty e^{-i\omega_n t} e^{i\omega_m t} e^{-kt} dt (Real)$$
$$= 1 - \frac{k}{N} \sum_{mn} Q^T_{mn} Q^S_{nm} \int_0^\infty cos[(\omega_m - \omega_n)t] e^{-kt} dt$$

$$\phi_S = 1 - \frac{1}{N} \sum_{mn} Q^T_{mn} Q^S_{nm} \frac{k^2}{k^2 + (\omega_m - \omega_n)^2} \tag{25}$$

We can compute the fractional yield with various direction of external magnetic field according to the equation above. For more complicated case in Figure-7, please refer to ref.[14](Supplementary Materials).

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