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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

姓　　名：骆锦威

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系　　别：生物系

专　　业：生物科学

指导教师：吴健生

2019 年 5 月 28 日

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

Jinwei Luo

（Department of Physics　Adviser：Jiansheng Wu）

［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 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 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 under total overcast instead of clear skies[3], many species are discovered to be able to sense earth magnetic field and use it for orientation[4]. Three possible mechanisms for magnetoreception are electromagnetic induction, magnetite-based mechanism and radical pair mechanism[5].

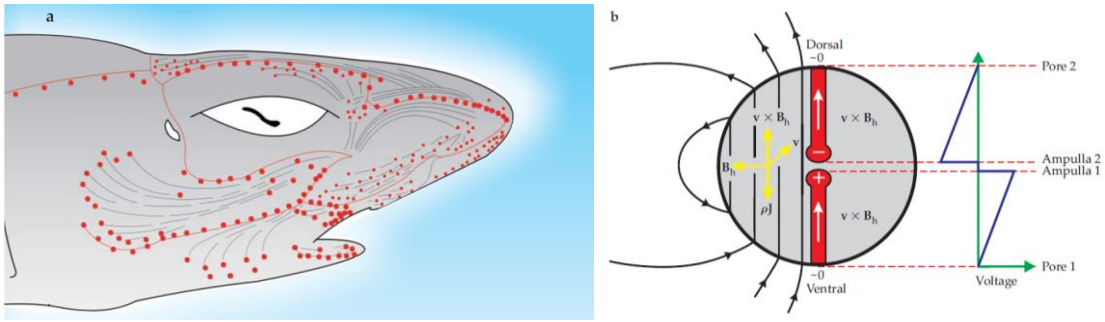

Figure-1 Electromagnetic induction mechanism in Chondrichthyes. (a) Ampullae of Lorenzini receptors(red dots) distribution in shark. **(b)** Voltage difference between two sides of an ampullae of Lorenzini due to electromagnetic induction, which causes a electric signal transduction. (modified after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

The electromagnetic induction occurs in a specialized organ called Ampullae of Lorenzini in cartilaginous fish such as sharks, rays and skates. Inside an ampullae of Lorenzini, there is an ion solution with good conductivity and with Jelly-filled pores that can accumulate electric voltage on two ampullas(Figure-1). The electric potential between two ampullas can induce a electric signal on electroreceptor cells that transduce the signal to the brain.

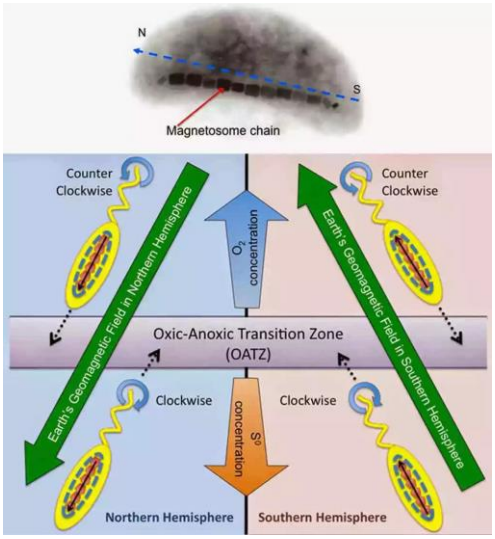

Figure-2 A magnetosome chain in magnetotactic bacteria. Magnetotactic bacteria(MTB) orientate their motion in vertical direction through magnetotaxis of a magnetosome chain. The OATZ towards which they use earth magnetic field to assist in their movement zone, is preferred by MTB.(modified after ref.[30])

Magnetite-based mechanism is well 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 assists the bacteria in moving upwards or downwards. These two mechanisms require special organs or particles in biological tissue that is rarely found in many other species.

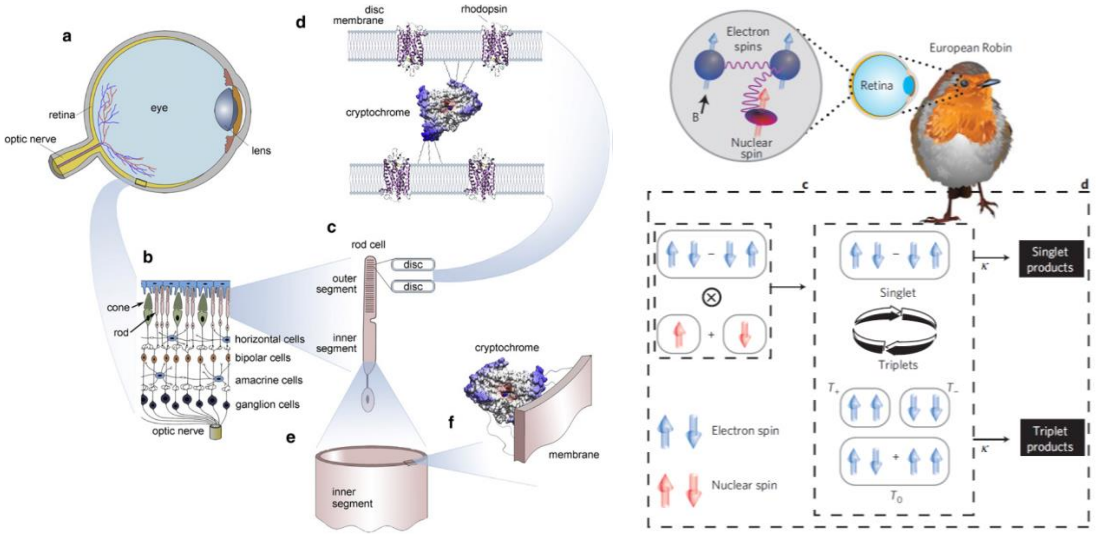

Figure-3 Schematic illustration of radical pair mechanism in bird's magnetoreception. (A)*left* The visual structure related to magnetoreception in cryptochrome protein. a)The electric signal transduction from retina to brain via optic nerve. b)Different cell types' organization on retina. c) Rods and cones

have a special arranged outer segment with a number of disk membranes. d)Predicted distribution of cryptochrome and opsin located in outer segments, which may account for magnetoreception. e) Inner segments in photoreceptor cells. f) cryptochrome distribution in inner segments.(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. Electron spins in a radical pair interact with nuclear spins in vicinity where hyperfine interactions occur. The angle-dependent Zeeman effect caused by earth magnetic field is related to anisotropic hyperfine interactions. (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]. A cryptochrome protein is the only protein that can form a light-induced radical pair on a flavin adenine dinucleotide (FAD) and tryptophan triad within it, which is the basis of radical pair mechanism. The cry4 protein, a member of cryptochrome family, is found recently located in the outer segment in cones on birds' retina(Figure-4)[7] and is considered to be a candidate to respond to earth magnetic field. Different wavelength of incident light and radiofrequency electromagnetic field can disrupt magnetic orientation of European robin[2,8-12,17]. Moreover, European robin derives their north direction by the smaller angle between the magnetic field vector and gravity vector rather than the polarity of the 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 in magnetoreception.

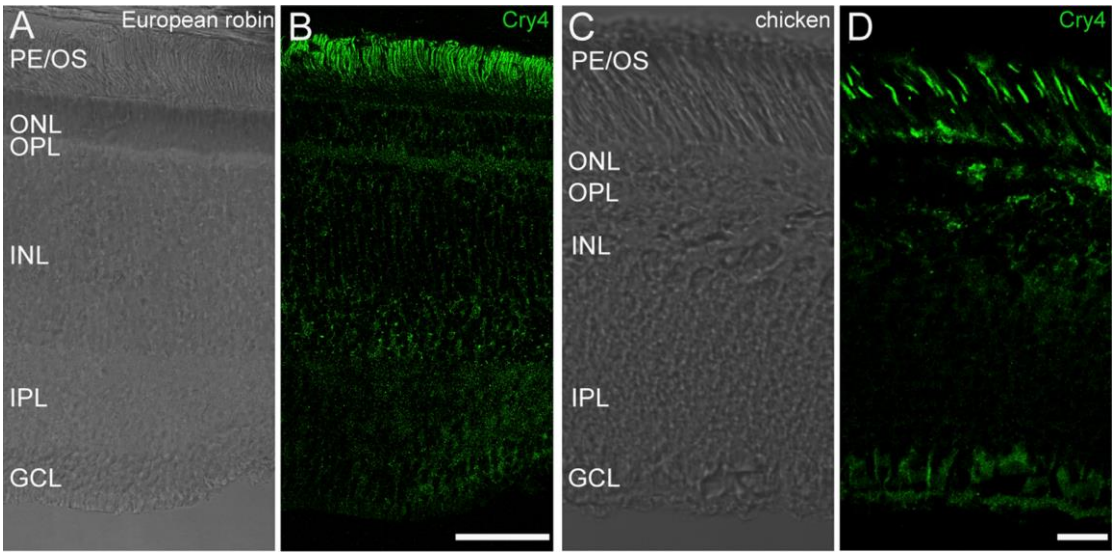

Figure-4 Cry4 is expressed in the outer segments in double cones and long wavelength single cones in the Retina of European Robin and Chicken. Bright field image **(A)(C)** and immunostaining **(B)(D)** of cry4 protein. (modified after ref.[7])

1.2 The radical pair mechanism

The radical pair mechanism was first proposed by Klaus Schulten, based on a quantum mechanical effects of radical pairs under steady 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]. Rhodopsin-like 1(Rh1) protein expressed in rod cells have a maximum absorption wavelength around 500nm while SWS1, SWS2, Rh2 opsin expressed in cones have maximum absorption wavelength of 355-455nm, 400-470nm and 480-520nm accounting for violet, blue and green light perception respectively.

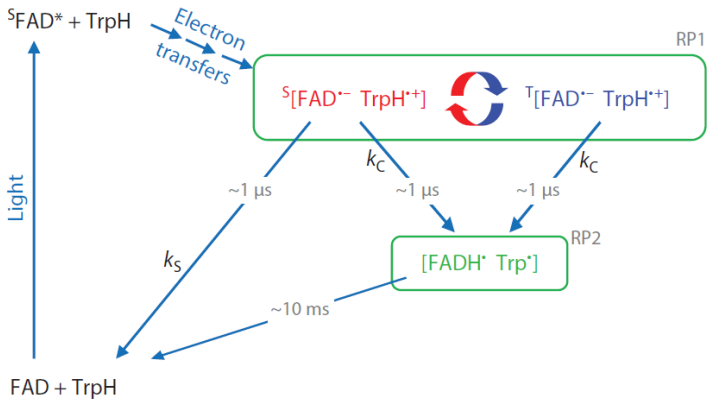

Figure-5 A FAD-TrpH radical pair formation and reactions in cryptochrome. After excited by an

incident photon, a FAD molecule is in an excited singlet state and an electron transfers from a tryptophan to a FAD molecule to form a transition state in singlet state. A singlet-triplet interconversion occurs due to hyperfine interactions. The singlet state rapidly recovers to ground state whereas triplet state react into a FADH-Trp radical pair via a change of protonation. The FADH-Trp radical pair recovers slowly into the ground state. (modified after ref.[1])

The radical pair mechanism are described below(Figure-5)[6]. Firstly, an incident photon hits on a FAD molecule and cause an electron transfer along the triad tryptophan onto FAD molecule forming unpaired electrons generating a pair of spins in singlet state. 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). It is a huge difference in lifetime of different radical pairs. Comparing to a short lifetime, a long lifetime of radical pair can keep the reactant in an excited state from inhibiting another photon absorption.

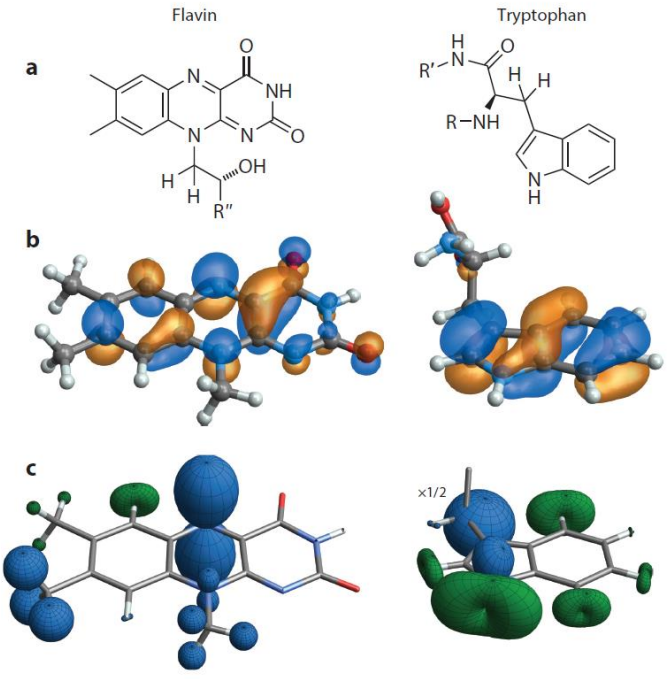

Figure-6 Molecular orbitals and hyperfine interactions in flavin and tryptophan radicals. On the left side it is flavin molecule while on the right side, it is tryptophan molecule. **(a)** Chemical structure. **(b)** Molecular orbitals. **(c)** Hyperfine interactions between nuclear and electron spins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

Secondly, the singlet-triplet oscillation occurs under hyperfine interactions and Zeeman

effect on the unpaired electron[6]. Hyperfine effect is due to the interaction between the electron spins and nuclear spins in vicinity whereas Zeeman effect is generated 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.

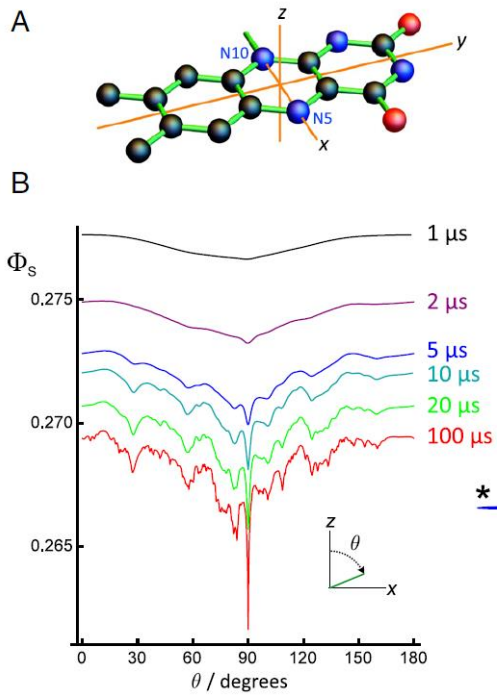

Figure-7 Simulation of the quantum effect of a FAD-Trp radical pair under external magnetic field. (A) The axis system on the flavin ring system. **(B)** Reaction yields of singlet radical pair [FAD•− TrpH•+]. θ is the angle of the external magnetic field in reference to the z-x plane of the flavin.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

Sensing the magnetic field in radical pairs is the first step converting magnetic information into variations of chemical lifetimes in biological system. And then, a secondary biological amplification is needed to convert the chemical signal into a biological detectable signal. The conventional hypothesis claims that different lifetimes of products 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. So we propose a novel biophysical model that can link the night vision and

radical pair mechanism in a direct way.

1.3 Visual system in vertebrates

A visual system of photoreceptor cells consists of three important components. One is a photoreception and a phototransduction cascade while the other is a visual cycle of rods and cones relating to recovery of 11-cis-retinal with Retinal Pigment Epithelial Cell(RPE). Another key component is sensitivity of incident photons and light intensity of minimal detectable contrast.

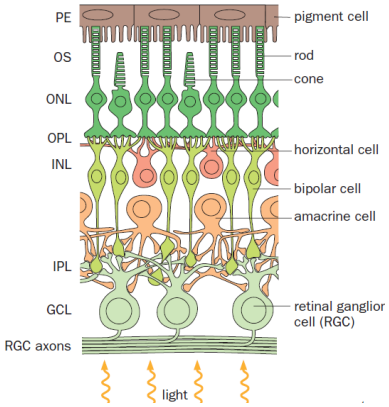

Figure-8 Organization of the retina. Photons input from the bottom. PE, pigment epithelium; OS, photoreceptor outer segments; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. (modified after ref.[19])

A specialized structure called outer segment in rods have a number of disk membranes on which opsins locate for maximizing light absorption(Figure-8,9[22]). A rod cell can be activated by a few photons under dark conditions[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 cells for dim light situation. To emphasize, cryptochrome protein such as cry4 expressed in birds' outer segment of cone cells may be a potential competitor with opsins for light absorption(Figure-4).

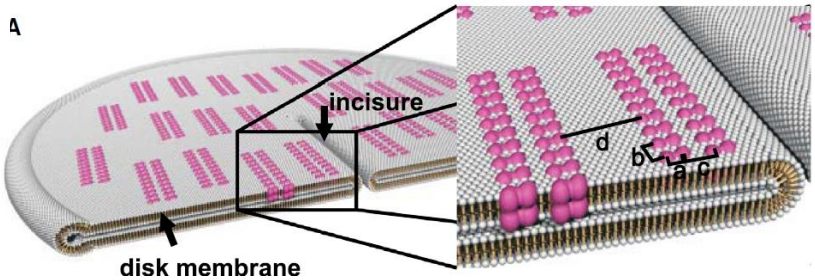

Figure-9 Model of rhodopsin distribution on the disk membrane. The number of rhodopsin on one

disk membrane is about 2100. According to the model, a=4nm; b=5nm; c=5nm; d=15nm on average. (modified after ref.[22])

The 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 cascade(Figure-10)[19]. A recovery from light-induced rhodopsin to ground-state rhodopsin has two influential factors: one is the recovery of signaling pathway and the other is the recovery of 11-cis-retinal known as a rod or cone visual cycle. The limiting step is the latter.

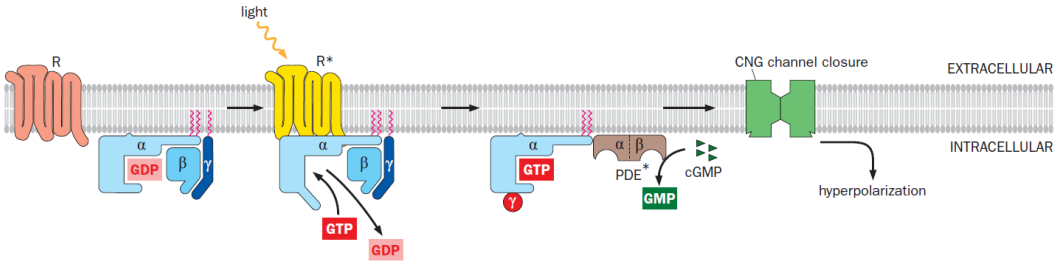

Figure-10 Phototransduction cascade. R^* represents an activated rhodopsin on a disk membrane of outer segments. After absorption of a photon, a GPCR protein release its β,γ subunits via GTP hydrolysis. The α subunit of GPCR will activate PDE(phosphodiesterase) to convert cyclic GMP into GMP. Decrease of cGMP leads to the closure of CNG channel generating a hyperpolarization on the membrane potential which causes an electric signal for visual formation. (modified after ref.[19])

The molecular pathway of a visual cycle of rods and cones as shown in Figure-11, is a dynamic biological pathway for formation and conversion of 11-cis-retinal[28]. A retinal is a chromophore in rhodopsin. After absorbing a photon, it is converted into an all-trans-retinal which can induce a conformational change of rhodopsin to have a downstream phototransduction cascade. The all-trans-retinal cannot absorb photons anymore, so it is removed by other proteins and transported to retinal pigment epithelial cells in order to convert the all-trans retinal back to 11-cis-retinal. After formation of 11-cis-retinal, it is transported back to outer segment of rods or cones and reassembled onto opsin to be a functional rhodopsin. A full visual cycle requires about 40 minutes for rods, whereas 2-3 minutes for cones[28].

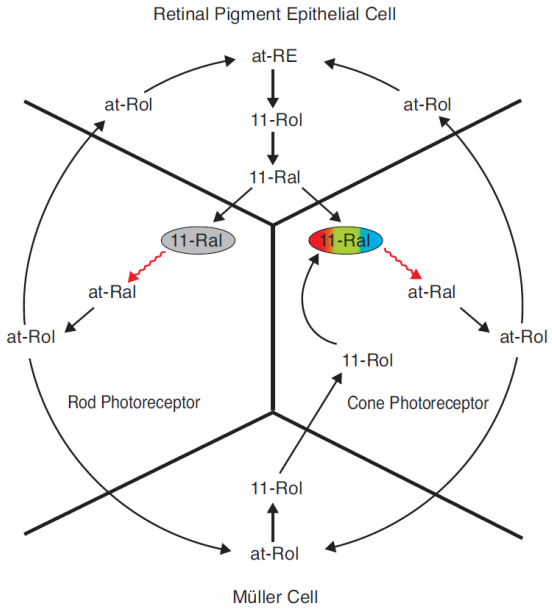

Figure-11 A visual cycle of rods and cones. In both rods and cones, after phototransduction, 11-cis-retinal is converted into all-trans-retinal and is dissembled from a rhodopsin. All-trans-retinal reacts into all-trans-retinol which is delivered into RPE(retinal pigment epithelial cell) to convert back into cis-retinal molecules. (modified after ref.[28])

For light intensity detection, animal eyes performed a complicated mechanism that 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 [15]. If the actual light stimulation is under this threshold, one could not distinguish the contrast before and after the stimulus, or in the center and in the vicinity. 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.

3.Biophysical model

We propose a new biophysical model that can directly explain how a magnetic sensor modulates photoreception of rhodopsin, namely Opsin-Cryptochrome Competition model(OCC model). Cryptochrome protein does not account for the phototransduction for vision, but it has capability to compete with rhodopsin to absorb photons which leads to a change of light intensity in rods or cones. Photoreceptor cells are sensitive to incident photons where the competition model relies on its light perception pattern. Here is a diagram of our model:

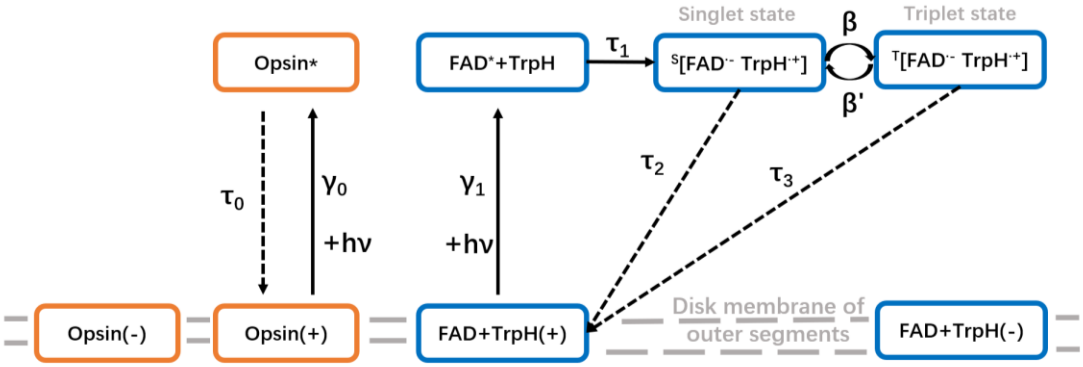

Figure-12 Opsin-Cryptochrome Competition Model. FAD and TrpH molecule are located in a cryptochrome protein while 11-cis-retinal is located in rhodopsin. These two molecules undergo a photon competition with a shared range of light wavelength within 450-550nm. Different symbols represent different states of molecules: (-) represents the ground state of molecules that have no light stimulation; (+) represents the ground state of a molecule absorbed 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.

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

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

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

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

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

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

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

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

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

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

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

According to our model, we build up a set of linear differential equations under several 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 since each cryptochrome have one FAD-TrpH molecule. We assume that no photon can escape from the absorption by opsin or cryptochrome, which implies photon number is a limiting factor. 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 derivatives(changing speed) of chemical concentration 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 obtain a quadratic equation(15) from equation(9). Two solutions for the quadratic equation can be solved and we take the solution equation(16) with a positive sign 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.

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

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

$$B = \tau_0\gamma_0 + 1 \quad (13)$$

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

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

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

3.2 Parameter initiation

The number of opsin equals to the number of cryptochrome (C_1:C_2=9:1). The *9:1* ratio is based on a rough estimation that in photoreceptor cells, the total mass of opsin in outer segment takes up near 90% of the total protein mass which implies cryptochrome is less than opsin by a factor of single digits. The actual number of opsin in the outer segment of one photoreceptor cell can be calculated by cryo-EM tomography(Figure-9)[22], which is approximately about thousand proteins per disk membrane. It is roughly two thousand disk membranes in the outer segment[28]. So the total number of proteins is around a million. The number of cryptochrome cannot be estimated due to lack of experimental results but recent finding shows cry4 protein is enriched in outer segment[7]. 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} for rods. We initialize C_1, C_2 and N_{photon} in the ratio of $9:1:10^{-2}$. Since rod cells are single photon detectors which might not have the photon

competition, so we simulate 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], A FAD-TrpH radical pair is estimated to have a lifetime about 1us. So we set the lifetime $\tau_2=1us$ whereas $\tau_3=10ms$ 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, the recovery time of retinal is 40 minutes for rods and 2-3 minutes for cones [28], which doesn't fit the actual frame rate of eyes which is about 30-60Hz. The frame rate is correlated with both the recovery of hyperpolarization to depolarization on membrane potential and the recovery of retinal in cone visual cycle, which is a limiting step. The reason why the recovery of a single rhodopsin cannot simply represent the recovery of all rhodopsin in outer segment is that the single molecular lifetime correlates to a whole cone visual cycle without considering the time evolution of retinal dynamics in each step. For 11-cis-retinal supply, photoreceptor cells continuously export an amount of trans-retinol molecules to retinal pigment epithelial cells but also import a large amount of 11-cis-retinal onto disk membranes to form functional rhodopsin[28]. The dynamics of this visual cycle cannot be reduced by a single retinal recovery cycle. So we use a macroscopic index that is the framerate of a bird's eye to define $\tau_0=5ms$ 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. 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 by a computational simulation from the research group of Peter Hore[14] whereas $\beta'=0$ due to no net conversion from triplet state to singlet state during a sufficient long time. Based on Figure-7, we can use equation $\beta = \frac{\Delta(\Phi_T)}{\Delta(t)}$ 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 $\beta = \frac{\Delta(\Phi_T)}{\Delta(t)}$, we can obtain the relationship between β and angle θ in Figure-13b.

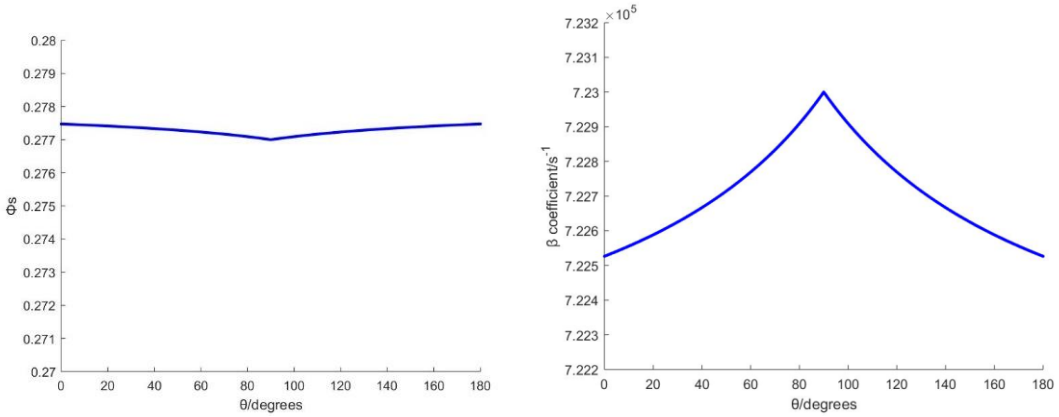

Figure-13 Fractional yield of singlet state and derived β coefficient under earth magnetic field with various angles. (a) *left:* Fractional yeild of singlet product with various θ derived from Figure-7B. **(b)***right:* β coefficient derived from (a) using the relation $\beta = \frac{1-\Phi_S}{\tau_2}$.

From Figure-13a, the fractional yield of singlet product has a smooth decline from 0° to 90° which represent the angle of the earth magnetic field and the 'z' direction of FAD molecule. Due to the same arrangement of FAD molecules on disk membrane in outer segment, the angle θ can represent the rotational angle of a bird's head. So, it is the head orientation that causes an angle difference between the FAD molecules and earth magnetic field. The orientation of FAD molecules results in different singlet-triplet oscillation patterns which leads to different β coefficient.

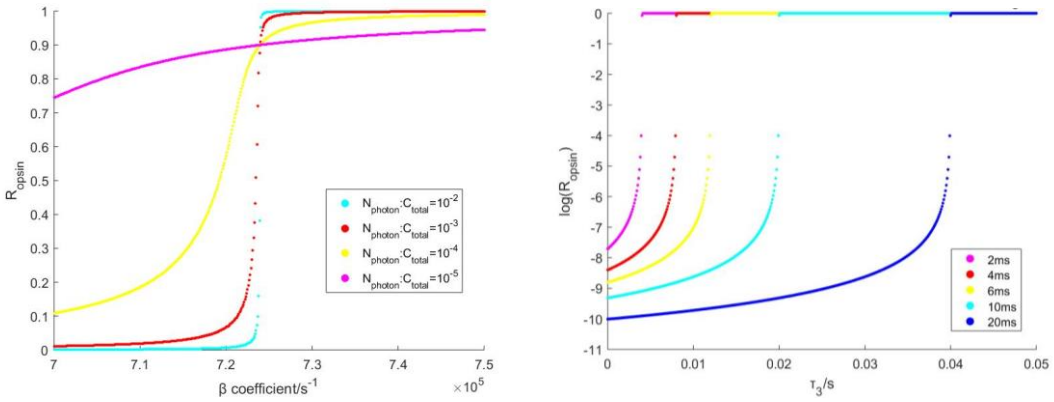

Figure-14 Photon competition of opsin and cryptochrome. (a)*left*: Photon absorption ratio with various β parameter under different ratio of incident photon numbers(N_{photon}) to total numbers of protein($C_{total}=C_1+C_2$). The R_{opsin} change more steeply when incident photon increases ranging from few photons to thousands photons. **(b)***right:* Logarithm of photon absorption ratio with change of τ_3 parameter under different opsin recovery time(τ_0). 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. The red curve in both (a) and (b) is simulation results based on OCC model. Parameter setting: $\tau_0=4.2ms$; $\tau_1=1ns$; $\tau_2=1us$; $\tau_3=10ms$; $\beta'=0$; $C_1:C_2:N_{photon}=9:1:10^{-2}$; $\gamma_0=\gamma_1=10^9/s$.

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(a) shows that the ratio steeply changed from 0 to 1 within a small range of β, which indicates an amplification effect of the competition model. The amplification effect is largely weakened when ratio of N_{photon} to C_{total} approaches to 0, which implies a lower photon threshold for photon competition model. This is another evidence that rod cell may not be the suitable photoreceptor cells accounting for photon competition. The steep region of the curve can be easily understood through equation(16). The denominator in equation(16) has a *A*-*B* term where the result can be changed dramatically when $A=B$. Coefficient *A* and *B* are two parameters correlating to rhodopsin cycle and FAD-Trp reaction cycle respectively. In Figure-14(b), the maximum amplification effect is largely influenced by opsin recovery time(τ_0). The longer recovery time results in a great decrease of amplification factor. Therefore, the amplification threshold is $\tau_0 \leqslant 5ms$, which fits our estimation in actual situation.

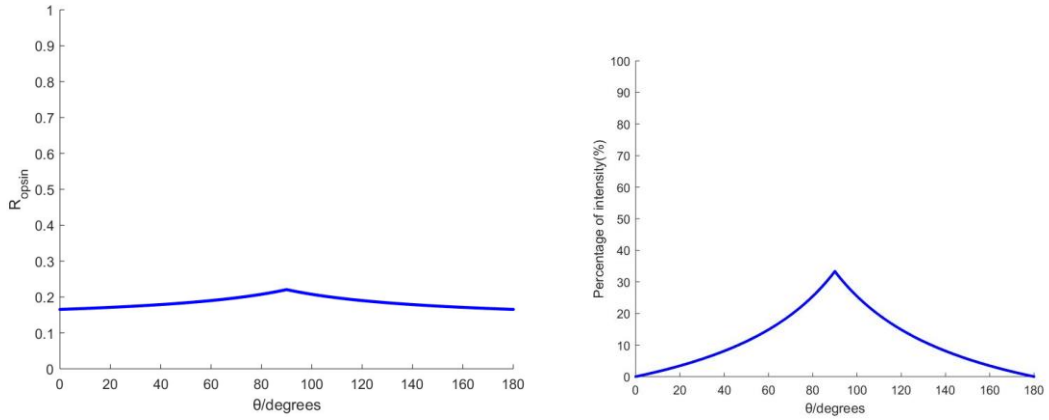

Figure-15 Photon absorption ratio and relative intensity change due to earth magnetic compass. **(a)***left:* Photon absorption ratio with change of θ. **(b)***right:* Light intensity difference over basal intensity at θ=0 change with various θ. Parameter setting: τ_0=*4.2ms;* τ_1=*1ns;* τ_2=*1us;* τ_3=*10ms;* β'=*0;* $C_1:C_2:N_{photon}=9:1:10^{-2}$; $\gamma_0=\gamma_1=10^9/s$. β is calculated in term of relationship in Figure-13(b).

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-15(a). Based on the light intensity response of photoreceptor cells, the increment threshold is around 14% for cones. From the light intensity change relative to the peripheral light intensity in reference to $\theta=0°$ shown in Figure-15(b), the Weber fraction at $\theta=90°$ can be up to 30%. That indicates a bird can distinguish the variation of light intensity due to a head rotation. Therefore, it is a simulated evidence to support our hypothesis that birds can "see" the magnetic field directly under the photon competition mechanism between opsins and cryptochrome. An illustration is shown in Figure-16 to simulate the intensity background change due to birds' head rotation.

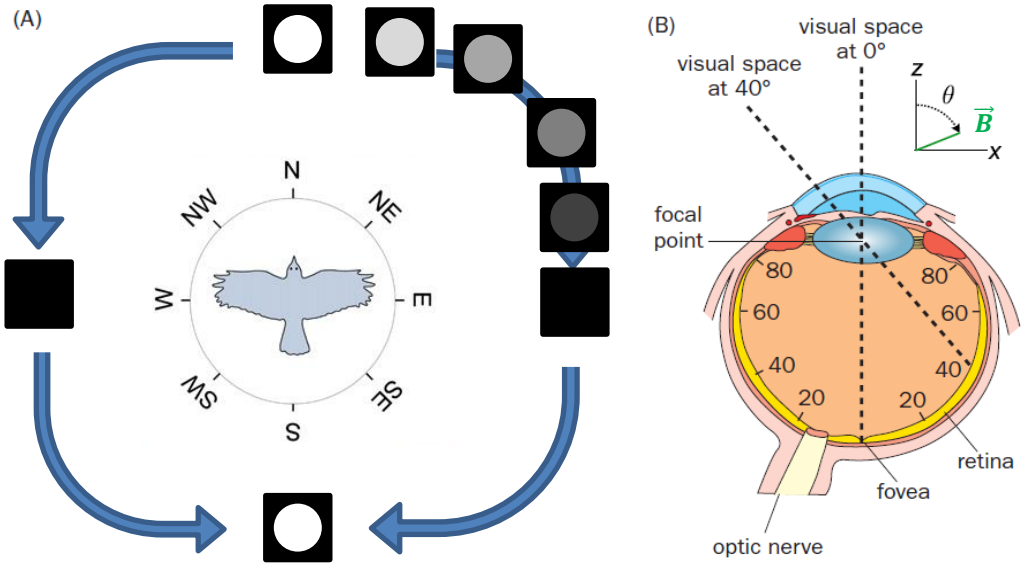

Figure-16 Illustration of birds' vision with head rotation. (A) Background intensity change with head rotation of a bird. This illustration is based on some assumptions. (B) We assume the 'z' direction of flavin molecule in Figure-7(A)is the same as visual space at 0°. Therefore, θ becomes the angle difference between the visual direction of birds' eyes and earth magnetic field direction. Figure-16(B) is modified after ref.[19].

4.Methods

Figures in 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 a 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 mechanisms in radical pair mechanism. The quantum effect of unpaired electrons can be the most potential candidates accounting for detection of earth magnetic field that is utilized by 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 night migration and navigation. Most species can response to earth magnetic field but lack of a clear behavioral purpose which adds difficulties for research. 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 be able 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. Two critical questions are proposed whether it is sufficient to detect earth magnetic field and whether it triggers a downstream sensory signaling. Earth magnetic field about 50uT is so

weak to generate a magnetic force of a magnetite. Models based on steady magnetic force in classical mechanics cannot explain animal magnetoreception. Therefore, it is a great 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 etc. 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. And it is known that different light wavelengths 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 absorb a photon and then produce a long-lived radical pair[1]. Therefore, cryptochrome in photoreceptor cells are considered 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 may be a side 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 based on four assumptions as following. First, the number of photon is limiting for both opsin and

cryptochrome indicating a full absorption of photons. Secondly, competition occurs in the outer segment in which opsin and cryptochrome are enrich. Thirdly, competition ability is evaluated by the number of functional rhodopsin and cryptochrome distributed on disk membranes implying that the recovery time of opsin and cryptochrome is a critical factor to influence the competition ability. Fourth, the alignment of flavin molecules in the outer segment is considered to be the same in one photoreceptor cell since disk membranes have highly-structural arrangements and are parallel to each other in outer segment.

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 reported 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

The model only works under the radical-based magnetoreception in migratory birds under total overcast and under dim light. The radical pair mechanism based on quantum spin dynamics has its limitation. The energy gap of singlet and triplet state is very small compared to molecular motions which indicates a short coherence time of spin dynamics. If thermal motions disrupt the singlet-triplet oscillation within 1 microsecond, no quantum effect is performed due to the decoherence of two electron spins. Till now, no experimental and theoretical work can determine the decoherence time of the spin. This is the biggest argument whether quantum mechanics plays a role in magnetoreception even in room temperature biological phenomenon. Despite of it, radical pair mechanism is still a competitive candidate in magnetoreception.

Our model has several estimated parameters that may lead to approximations to the real situation. 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. The lifetime of the radical pair product is simply estimated without solid theoretical computation or experimental measurement such as τ_2 and τ_3. The approximated rate constant β need to be calculated by quantum transition state theory where here we simply treat it 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 11-cis-retinal and all-trans-retinal is complicated which involves the assembly rate of retinal onto opsin, the concentration of retinal in outer segments, diffusion velocity of retinal and removal rate of retinal molecule from rhodopsin. Each of those physical quantities can affect the actual recovery time of rhodopsin. In order to model this process, a simplified parameter τ_0 is estimated as the frame rate of a human eye. Finally, 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.

5.3 Experimental predictions

One important prediction of our model is that cone cells are the photoreceptors for magnetoreception since the photon competition is valid in cones rather than rods.

From simulation results, the photon number is vital for visual modulation under earth magnetic field. So there exists a upper and lower thresholds of incident photon that determine the effectiveness of magnetic compass. Controlled experiment of incident light intensity on magnetic compass will help prove or disprove our theoretical model.

Besides, according to OCC model, magnetic field perception is a pure visual consequence of variations in background intensity. Disruptions or analogy of background intensity can be performed in the experiment. For example, an apparatus that can freely change the incident light intensity from different incident angle is used to disrupt the original background intensity pattern due to earth magnetic field. Such apparatus can detect the direction of the earth magnetic field and automatically adjust the light intensity in the same direction. The light intensity difference caused by magnetoreception and the apparatus will be balanced out which disrupts the magnetic perception.

5.4 Summary

Magnetoreception has been investigated for about half of a century. None of the three mechanisms are complete models for magnetic sensing. Among them, the radical pair mechanism has an increasing evidences in support of the bird magnetoreception such as European robin and pigeon.

We proposed a novel biophysical model namely OCC model accounting for a direct connection between a radical-pair based magnetic compass and a biological response in birds' vision. A secondary amplification effect is found based on our simulation results. More experiments are needed to confirm theoretical predictions.

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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.

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

$$\begin{aligned} &= \frac{1}{N} Tr[Q^T e^{-\frac{iHt}{\hbar}} Q^S e^{\frac{iHt}{\hbar}} e^{-kt}] \\ &= \frac{1}{N} \sum_{mn} \langle m| \left[Q^T |n\rangle \langle n| e^{-\frac{iHt}{\hbar}} Q^S e^{\frac{iHt}{\hbar}} e^{-kt}\right] |m\rangle \\ &= \frac{1}{N} \sum_{mn} \langle m| Q^T |n\rangle e^{-\frac{iHt}{\hbar}} \langle n| Q^S |m\rangle e^{\frac{iHt}{\hbar}} e^{-kt} \\ &= \frac{1}{N} \sum_{mn} \langle m| Q^T |n\rangle e^{-i\omega_n t} \langle n| Q^S |m\rangle e^{i\omega_m t} e^{-kt} \end{aligned} \tag{23}$$

We can let:

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

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

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

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

We can compute the fractional yield with various direction of external magnetic field according to the equation above. For a more complicated case, please refer to ref.[14].

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