Angular Precision of Radical Pair Compass Magnetoreceptors

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ABSTRACT The light-dependent magnetic compass sense of night-migratory songbirds is thought to rely on magnetically sensitive chemical reactions of radical pairs in cryptochrome proteins located in the birds’ eyes. Recently, an information theory approach was developed that provides a strict lower bound on the precision with which a bird could estimate its head direction using only geomagnetic cues and a cryptochrome-based radical pair sensor. By means of this lower bound, we show here how the performance of the compass sense could be optimized by adjusting the orientation of cryptochrome molecules within photoreceptor cells, the distribution of cells around the retina, and the effects of the geomagnetic field on the photochemistry of the radical pair.

INTRODUCTION

Night-migratory songbirds have a light-dependent magnetic compass sense that helps them navigate the thousands of kilometers that separate their breeding and wintering grounds (1–3). How this compass works is something of a mystery (4). Currently, the leading hypothesis for the primary detection event involves the photochemical production of transient radical pairs in cryptochrome proteins contained in the birds’ retinas (5–7). The spin dynamics of these paramagnetic reaction intermediates could provide a mechanism by which the direction of the Earth’s magnetic field (~50 μT) is encoded in the quantum yield of a signaling state of the protein.

Light is a crucial component of this hypothesis (8,9). Blue light is required to excite the flavin chromophore and trigger the intraprotein electron transfers that generate the radical pairs (5). A fundamental question, therefore, is whether this mechanism is viable given the dim light conditions experienced by nocturnal migrants. This issue has recently been addressed by Hiscock et al. (10), who used an information theory approach to obtain a strict lower bound on the angular precision with which a bird could orient itself using a cryptochrome-based radical pair sensor. The method has the advantage that it avoids having to make guesses about the nature and efficiency of signal transduction and postprocessing in vivo, instead calculating the best-case precision. It was concluded that the average photon flux on a cloudless and moonless night (~3 × 10^-4 lux (11)) might not be sufficient for at least some of the currently considered radical pair models.

In this work, we extend this analysis and attempt to answer four main questions. 1) How does the angular precision of a radical pair compass depend on the total number of photons absorbed per second by cryptochromes in the eye? 2) Can the precision of such a compass be improved by optimizing the orientation of the proteins inside photoreceptor cells in the retina? 3) Could the angular precision be increased by concentrating the cells that contain
magnetoreceptors in certain regions of the retina? 4) How does the angular precision depend on the magnetic and kinetic properties of the radicals?

METHODS

Eye model

Following Hiscock et al. (10) and Lau et al. (12), we model the bird’s eye as a sphere comprising a hemispherical retina and a pupil positioned diametrically opposite its center (Fig. 1 a). Cylindrical receptor cells are distributed around the retina with their symmetry axes pointing toward the center of the sphere. Their locations are specified by angles $\kappa$ (co-latitude) and $\varphi$ (azimuth), with $\kappa = 0$ at the center of the retina and $\kappa = 90^\circ$ at its periphery (Fig. 1 b). The optical axis of the eye is constrained to the horizontal plane. The direction of the geomagnetic field inside a given cell is therefore determined by $\kappa$ and $\varphi$ and by the direction of the optical axis, referred to as the “head direction,” $\theta$ (Fig. 1 b). Although a crude approximation to reality, this geometry captures the essential physics.

There could be more than a million cells in the retina containing magnetoreceptor molecules—far too many to model explicitly (10). To reduce the computational burden, Hiscock et al. treated clusters of neighboring cells, referred to as grouped receptor cells, each of which absorbs the total number of photons that would have been absorbed by the individual cells in the cluster in a given time interval (10). The assumption here is that the cells within a group are sufficiently close together that they have almost identical orientations and therefore very similar responses to the geomagnetic field (13). The number of these groups of cells is denoted $r$. Hiscock et al. generated a 180 $\times$ 180 square grid of points on a plane tangent to the center of the retina, which was then mapped onto the retina by means of a stereoscopic projection using the pupil as the point of perspective (10). The result was an array of 25,132 grouped cells covering the whole retina. As we shall see below, accurate estimates of the head direction error can in fact be obtained with far fewer grouped cells. To avoid the higher-than-average density of cells near the edges of the retina resulting from the stereoscopic projection, we distribute cells here using the SpherePoints function in Mathematica (14), which places points on the surface of a sphere so that they are approximately equally spaced. In practice, this change was found to make little difference to the calculated head direction errors provided $r > 100$. Every grouped cell is assumed to absorb the same number of photons per second irrespective of both the head direction and the position of the cell in the retina. Every photon absorbed is assumed to give rise to a radical pair. All the cells and their contents are assumed to be identical. The signal from each receptor cell is an average over the radical pairs within it.

Receptor molecules

The radical pair model of compass magnetoreception is based on the formation of light-induced radical pairs in aligned receptor molecules, generally assumed to be cryptochrome proteins, contained in cells in the retina (6,12). The response of a cell to the geomagnetic field is encoded in the yield of a signaling state of the protein produced by chemical reactions of these radical pairs (15). The amplitude of this signal, given the symbol $\Phi_S$, depends on the direction of the magnetic field with respect to the proteins which are assumed to have identical intracellular orientations. The direction of the geomagnetic field with respect to the receptor molecules is therefore completely determined by $\theta$ (the head direction), by $\varphi$ and $\kappa$ (the position of the cell in the eye), and by the orientation of the proteins within the cell.

We base the calculations here on a model of the $[\text{FAD}^{\mathrm{+}}-\text{TrpH}^{\mathrm{+}}]$ radical pair formed in cryptochrome by electron transfer along a triad or tetrad of tryptophan (TrpH) residues to the photoexcited singlet state of the noncovalently bound flavin adenine dinucleotide (FAD) chromophore. Although magnetic field effects have been reported for a few purified cryptochromes and are generated by $[\text{FAD}^{\mathrm{+}}-\text{TrpH}^{\mathrm{+}}]$ radical pairs (16,17), it has not yet been possible to measure the dependence of the quantum yield of a potential signaling state on the direction of an external magnetic field. Following Hiscock et al. (10), we therefore base these calculations on spin dynamics simulations of $[\text{FAD}^{\mathrm{+}}-\text{TrpH}^{\mathrm{+}}]$. Previous work has shown that $\Phi_S$ is dominated by the axial hyperfine interactions of two nitrogen nuclei in FAD (18,19) such that $\Phi_S$ has an approximately axial symmetry around the normal to the plane of the isoalloxazine group of the flavin (denoted the $z$ axis). The anisotropy of $\Phi_S$ is therefore determined by the angle, $\zeta$, between the flavin $z$ axis and the direction of the geomagnetic field experienced by the radical pair. We assume perfect axial symmetry here. As a result, only two angles are required to specify the orientation of the cryptochrome molecules within a cell: the co-latitude, $\beta$, and the azimuth, $\alpha$. When $\beta = 0$, the magnetic symmetry axis of the flavin ring system in a cryptochrome molecule is parallel to the symmetry axis of the cell that contains it, and the cell axes point toward the center of the eye. Fig. 1 c shows the three molecular orientations considered below: O1 ($\beta = \pi/2$, $\alpha = \pi/2$), O2 ($\beta = \pi/2$, $\alpha = 0$), and O3 ($\beta = 0$).

Following Hiscock et al. (10), we use a simple parameterized model of the dependence of the yield of the signaling state on $\zeta$:

$$\Phi_S(\zeta) = a - b \exp \left[ \frac{(\zeta - 90^\circ)^2}{2c^2} \right]. \quad (1)$$

This form of $\Phi_S(\zeta)$ is an inverted Gaussian, centered at $\zeta = 90^\circ$, with offset $a$, amplitude $b$, and half-width $c$ and default values $a = 0.5$, $b = 0.3$.
yield signals and so leads to the best-case compass precision. For details of the theory, the reader is referred to (10).

**Lower bound error in the head direction**

Hiscock et al. derived the following expression (a rearranged form of their Eq. S19) for $\epsilon_H$, the lower bound on the root mean-square error in the head direction estimate obtained from an encoding of the true head direction by molecules in cells distributed around the retina (10):

$$\epsilon_H = \sqrt{\frac{2\pi}{e \det(\Sigma)}} \exp \left[ \sum_{i=1}^{r} \ln(\sigma_{i,\theta}^2) \right].$$  \hspace{1cm} (5)

We refer to $\epsilon_H$ here as the lower bound error in the head direction. In Eq. 5, $\Sigma$ is the $r \times r$ covariance matrix with elements

$$\Sigma_{ij} = \left( \Phi_{S}^{\theta} \Phi_{S}^{\theta} \right) - \left( \Phi_{S}^{\theta} \right) \left( \Phi_{S}^{\theta} \right) + \delta_{ij} \sigma_{i,\theta}^2,$$  \hspace{1cm} (6)

in which $\Phi_{S}^{\theta}$ is the signal for cell $i$ and head direction $\theta$, $\delta_{ij}$ is the Kronecker delta, and

$$\sigma_{i,\theta}^2 = \frac{1}{p} \Phi_{S}^{\theta} \left( 1 - \Phi_{S}^{\theta} \right),$$  \hspace{1cm} (7)

with $p$ the number of photons absorbed per grouped receptor cell in a certain time interval. The overbars indicate an average over all head directions ($0 \leq \theta < 2\pi$) in the horizontal plane.

The fundamental quantity on which Eq. 5 is based is the mutual information between the actual head direction and the estimated head direction. This is a measure of how much uncertainty there is in the output of the information channel for a given input (26). This is obviously impractical to calculate, and so we use the data processing inequality (27,28) to place an upper bound on the mutual information (which translates into a lower bound in the error in the head direction estimate). The assumption invoked in using this relation is that the sole source of magnetic information available to the bird is contained within the reaction yield signal and that the estimate of the head direction relative to an external magnetic field is constructed using only this information. The signaling pathway therefore forms a Markov chain, and the maximal possible information available at the output is equal to the information contained in the encoded input, i.e., the total information contained in the reaction yield signal.

This mutual information can be related to the lower bound heading error through the Shannon entropy (23) of the head direction estimate, which is the formal quantity in the context of information theory that measures uncertainty in a variable. Because this entropy is bounded by a closed form expression in terms of the variance of the variable distribution, after some manipulations (10) we can come to an expression for $\epsilon_H$ in terms of the mutual information between the head direction and the single yield signal. On substituting expressions to calculate the mutual information (Supporting Material of (10)), we arrive at Eq. 5.

To summarize, the following steps are required to calculate $\epsilon_H$ for a given choice of $\Phi_{S}^{\theta}$, $r$, $p$, and receptor orientation: 1) determine $\kappa$ and $\nu$ for each of the $r$ receptor cells, 2) Calculate $\cos^{\theta}\Phi_{S}$ (Eqs. 2, 3, or 4) and hence $\Phi_{S}^{\theta}$ (Eq. 1) for each cell for each of $K = 1000$ equally spaced values of $\theta$ between 0 and $2\pi$, 3) Obtain $\left( \Phi_{S}^{\theta} \right)$, $\left( \Phi_{S}^{\theta} \right)^2$, and $\ln(\Phi_{S}^{\theta})$ by averaging over $\theta$. 4) Use Eqs. 5, 6, and 7 to compute $\epsilon_H$. Numerical errors arising from very small values of both $\det(\Sigma)$ and the exponential term in Eq. 5 can be avoided by multiplying all elements of $\Sigma$ by $s = \left(1 - (1 - \nu)\right)^{-1}$ and adding $\ln(\nu)$ to the argument of the exponential in Eq. 5, where $\nu$ is the offset in the model signal (Eq. 1).
Migratory songbirds can detect the axis of the geomagnetic field with an accuracy better than 5° (29,30). For the purposes of this work, we consider as viable a model compass for which $\epsilon_{H} < 5°$.

RESULTS AND DISCUSSION

Dependence of $\epsilon_{H}$ on total number of photons

The precision with which radical-pair-based sensors can determine a magnetic compass bearing should improve as either the number of receptor cells, $r$, or the number of photons absorbed by each cell, $p$, is increased. To explore this dependence in more detail, we calculated $\epsilon_{H}$ for a range of values of $r$ and $p$ using the default model signal in Eq. 1 and a uniform distribution of cells across the retina. Fig. 2 shows $\epsilon_{H}$ for orientation O1 as a function of $r$ for four values of the product $rp$. Similar results were found for orientations O2 and O3 (Fig. S1). Provided $r > 100$, $\epsilon_{H}$ is independent of $r$ for a fixed value of $rp$ and decreases as $rp$ is increased. That is, when there are more than $\sim 100$ grouped receptor cells, the precision of the compass bearing is determined by the total number of photons absorbed across the whole retina, i.e., the total number of photo-induced radical pairs. One of the implications of this finding, which only seems to break down when 1) the offset is outside the range $0.1 < a < 0.9$, 2) the amplitude of the signal is unrealistically large (e.g., $b > 0.1$), or 3) its width is exceedingly narrow (e.g., $c < 0.1°$), is that it is harmless to model large groupings of cells. This finding validates the concept of grouped receptor cells as proposed by Hiscock et al. (10) and greatly reduces the computational burden. The conclusion that $rp$ is the important factor in determining $\epsilon_{H}$ also holds true for any specified region of the retina as long as the grouped receptor cells are uniformly distributed within that region (Fig. S2).

The total number of photons ($rp$) impinging on the double cone photoreceptor cells in the eye of a small songbird on a clear moonless night may be estimated as follows: each cell receives $\sim$1 photon per second (5), there is one cell per $\sim 40 \mu m^2$ of retina (31), and the radius of the hemispherical retina is $\sim 4$ mm (32). Combining these numbers gives $rp \approx 3 \times 10^8$ s$^{-1}$. It seems likely that the signal-to-noise ratio of magnetic sensing could be improved by integrating the signal over a short period of time. An estimate of this time comes from experiments in which birds that had been exposed to eastward-rotated magnetic fields during the twilight period before take-off were observed to fly westward instead of the northerly direction of birds that had experienced the ambient geomagnetic field (11). Quoting Cochran et al., “Our data suggest that the time it takes Catharus thrushes to determine a magnetic compass direction while aloft must be relatively short, because we recorded several headings of treated birds within a few minutes after take-off and all of these headings were already deflected” (11). From this, we infer an integration period of no more than $\sim 100$ s such that the total number of photons, and therefore radical pairs, required to obtain a compass bearing could be on the order of $3 \times 10^8$. As can be seen from Fig. 2, $rp = 3 \times 10^8$ is just about sufficient to achieve a lower bound of 5° when using the default model signal (Eq. 1).

Dependence of $\epsilon_{H}$ on receptor orientation

Fig. 3 shows $\epsilon_{H}$ for the three orientations O1–O3 in Eqs. 2, 3, and 4, again using the default parameters for $\phi_S(\zeta)$ in Eq. 1. All three give $\epsilon_{H} = \sqrt{2\pi/e}$ radians $= 87.1°$ in the limit of small $rp$, dropping down to zero for large $rp$. For intermediate values of the total number of photons, O2 and O3 give very similar $\epsilon_{H}$-values that are significantly smaller than those for O1 for all values of $rp$ between $\sim 10^6$ and $\sim 10^8$. For example, to achieve a lower bound of 5°, $rp$ must be $2.28 \times 10^6$ for O1, $5.26 \times 10^7$ for O2, and $5.42 \times 10^7$ for O3, i.e., in the ratio

![Figure 2](image-url)  
**FIGURE 2**  
Lower bound error calculated using the default model signal (Eq. 1 with $a = 0.5, b = 0.00127$, and $c = 26°$), as a function of the number of grouped receptor cells for four values of $rp$, the total number of photons absorbed across the retina.

![Figure 3](image-url)  
**FIGURE 3**  
Lower bound error as a function of $rp$ for the three orientations, O1–O3, using the default model signal (Eq. 1). The corresponding values of $\epsilon_{H}$ for O1 shown in Fig. 4, $c$ and $e$ of Hiscock et al. (10) were calculated using half of the available information (i.e., $-90° < \theta < 90°$) so that artificial processing routines could be used to estimate the attainable heading accuracy. For this reason, the values of $\epsilon_{H}$ presented here, which use all the available information ($-180° < \theta < 180°$), are larger by a factor of 2.
4.33:1.00:1.03, respectively. O1, which gives the least precise compass bearing, is the orientation chosen by Hiscok et al. to assess the performance of different cryptochrome-based radical pairs (10). It appears that O2 and O3 are very close to optimal. Although we were able to find orientations for which $\varepsilon_H$ is slightly smaller than for O2 and O3, this was only possible for values of $rp$ for which the compass is very imprecise (e.g., $\varepsilon_H > 10^{-9}$, Fig. S3). Using the default model, we were unable to find an orientation that gave a poorer performance than O1 for any value of $rp$.

The dependence of $\varepsilon_H$ on $rp$ was found to be reasonably well described by the empirical expression

$$\varepsilon_H \approx \frac{2\pi}{e} \left( \frac{1}{1 + a_1 rp + (a_2 rp)^2} \right).$$

(8)

Good agreement with the data in Fig. 3 is obtained with the following values of $a_1$ and $a_2$:

- O1: $a_1 = 2.718 \times 10^{-7}$, $a_2 = 0.659 \times 10^{-7}$;
- O2: $a_1 = 3.044 \times 10^{-7}$, $a_2 = 2.363 \times 10^{-7}$;
- O3: $a_1 = 3.208 \times 10^{-7}$, $a_2 = 2.348 \times 10^{-7}$.

(9)

**Origin of differences between orientations**

We have shown above that $\varepsilon_H$ is affected by the orientation of the radical pairs within the receptor cells and that O1 performs significantly less well than O2 and O3. Some insight into these differences can be obtained by considering the variation of the signal strength, $\Phi_S(\nu, \kappa)$, across the retina by means of stereographic projections of the retina onto a disk tangent to the center of the retina using the pupil as the point of perspective. When the projected function is $\Phi_S(\nu, \kappa)$, these projections have been called visual modulation patterns (VMPs) (6). Fig. 4 shows VMPs of the default signal for five head directions and the three receptor orientations. In these plots, the dependence of $\Phi_S(\nu, \kappa)$ on $\kappa$ (co-latitude) and $\nu$ (azimuth) is represented, respectively, by radial and angular variations in the VMP. The center of the retina ($\kappa = 0$) projects to the center of the VMP. In all three cases, the pattern changes with head direction, providing information on the horizontal component of the geomagnetic field. Although the patterns are quite different for the three orientations, it certainly is not clear from Fig. 4 why O2 and O3 are better than O1 in terms of providing a precise compass bearing.

The lower bound error generated by a given pattern of receptor cells and a given orientation of radical pairs within
them is the result of integrating the information available from each of the cells. Hence, the fact that different radical pair orientations result in different values of $\epsilon_{H}$ must be reflected at the level of individual receptors. We refer to the $\epsilon_{H}$ generated by a pattern of $r$ receptors absorbing $p$ photons per receptor as the joint lower bound, and the $\epsilon_{H}$ generated by any one of the $r$ receptors absorbing $rp$ photons as the individual lower bound, denoted $\epsilon_{I}(r, \kappa)$. The calculation of $\epsilon_{I}(r, \kappa)$ for a receptor cell located at position $(r, \kappa)$ on the retina can be divided into three steps: 1) find the angle $\zeta(r, \kappa)$ between the geomagnetic field and the symmetry axis of the radical pairs bound inside the cell, as a function of the head direction $\theta$, using Eqs. 2, 3, and 4; 2) find the signal $\Phi_{B}(r, \kappa)$ from this cell, again as a function of $\theta$, using Eq. 1; 3) calculate $\epsilon_{I}(r, \kappa)$ using Eq. 5 with $r = 1$. We now investigate the connections among these steps using the same projection as in Fig. 4 to visualize, initially, $\epsilon_{I}(r, \kappa)$ instead of $\Phi_{B}(r, \kappa)$.

Starting from step 3 above, Fig. 5 a shows the projection of $\epsilon_{I}(r, \kappa)$ for each of the three orientations with $rp = 3 \times 10^{9}$. In each case, there is a curve of minimal $\epsilon_{I}(r, \kappa)$ (violet), which is X-shaped for O1, 8-shaped for O2, and $\pi$-shaped for O3. We shall call this the “minimal curve” on the retina surface. The patterns in Fig. 5 a bear a clear resemblance to the corresponding projections of $\Phi_{B}(r, \kappa)$ in the middle row of Fig. 4.

Moving up to step 2, Fig. 5 b shows the projections of the standard deviation of $\Phi_{B}(r, \kappa)$ over all head directions. These patterns also closely resemble the corresponding projections in Fig. 5 a. In particular, the minimal curves exactly agree (note that the color code in Fig. 5 b has been inverted for an easier comparison with Fig. 5 a). This means that, somewhat surprisingly, almost all the relational information contained in Fig. 5 a is captured by Fig. 5 b without having to calculate any $\epsilon_{I}(r, \kappa)$ values.

One step up further, Fig. 5 c (again with an inverted color code) shows the stereographic projections of the function

$$A(r, \kappa) = \max_{\theta_0 \in [0, 2\pi]} |\cos \zeta(r, \kappa)| - \min_{\theta_0 \in [0, 2\pi]} |\cos \zeta(r, \kappa)|,$$

where $\zeta(r, \kappa)$ is the angle between the magnetic field axis and the symmetry axis of the radical pairs in the cell at position $(r, \kappa)$ in the retina. All relational information is once again almost completely captured, even without having to calculate $\Phi_{B}(r, \kappa)$. The reason why different orientations lead to different joint lower bounds may therefore be traced back to Eq. 10; the greater the variation in $|\cos \zeta(r, \kappa)|$ as the eye scans the horizon, the greater the variation in $\Phi_{B}(r, \kappa)$, and therefore the greater precision with which the geomagnetic field direction can be determined.

A feature of the individual lower bound errors in Fig. 5 a is that for all three radical pair orientations, the maximal and minimal values of $\epsilon_{I}(r, \kappa)$ are the same $(87.1$ and $50.3^\circ$, respectively). The latter corresponds to the minimal curve mentioned above. We therefore wondered whether orientations O2 and O3 are able to generate a smaller joint lower bound because more cells have individual lower bounds close to the minimum. To test this, we defined the essential region for a given radical pair orientation as the region surrounding the minimal curve on the retina surface in which every point has an $\epsilon_{I}(r, \kappa)$ that differs from the minimal $\epsilon_{I}(r, \kappa)$ by less than $27.8\%$. The reason for choosing $27.8\%$ is explained by means of Figs. S4 and S5. The essential regions for the three orientations are shown in Fig. 6. Their relative areas are $O1:O2:O3 = 1.0:2.3:1.5$, supporting the above conjecture. Table 1 compares

![FIGURE 5 Stereographic projections of (a) $\epsilon_{I}(r, \kappa)$, (b) the standard deviation of $\Phi_{B}(r, \kappa)$, and (c) $A(r, \kappa)$ using the default model signal for the three orientations, O1–O3.](image)

![FIGURE 6 Representations of the model eye showing the essential regions (green) for the three orientations, O1–O3, superimposed on the retina (yellow/orange). The pupil is shown as a blue disk.](image)
TABLE 1 Joint Lower Bounds for Different Distributions of Cells in the Retina

|                | O1      | O2      | O3      |
|----------------|---------|---------|---------|
| Whole retina $\varepsilon_{H}$ | 12.4°   | 1.5°    | 2.6°    |
| Essential region $\varepsilon_{H}$ | 4.0°    | 0.8°    | 0.6°    |

Parameters: $a = 0.7$, $b = 0.00381$, $c = 10°$, and $rp = 3 \times 10^{5}$.

aLower bound error when the receptor cells are uniformly distributed across the whole retina.
bLower bound error when the receptor cells are uniformly distributed in the essential region for each orientation.

dependent on the amplitude, $b$, is relatively simple; $\varepsilon_{H}$ is a function of $b^2rp$ only (Fig. S6). That is, if the amplitude of the signal is doubled, four times fewer photons in total are required to achieve the same $\varepsilon_{H}$. Under similar conditions, O2 and O3 exhibit the same kind of dependence on $a$, $b$, and $c$ but generally give smaller values of $\varepsilon_{H}$ (as noted above for the default signal).

There is thus considerable scope for optimizing the properties of the radicals and their orientation in the receptor cells to improve the precision of the compass bearing. This point can be illustrated by making stepwise changes in the parameters to reduce the number of photons required to achieve $\varepsilon_{H} = 5°$. Fig. 8 shows $\varepsilon_{H}$ for six cases (see Table 2) starting with O1 and the default values of $a$, $b$, and $c$ and ending at O2 with $a = 0.9$, $b = 0.00508$, and $c = 10°$. Making these relatively modest changes to the model signal and choosing orientation O2 in preference to O1 reduces the total number of photons required for $\varepsilon_{H} = 5°$ by a factor of almost 600 and reduces the value of $\varepsilon_{H}$ predicted for $rp = 3.94 \times 10^{5}$ photons from 82.7 to 5° (Table 2).

This value of $rp$ is considerably smaller than the estimated number of available photons ($3 \times 10^{5}$; see above).

CONCLUSIONS

We have investigated the angular precision of the light-dependent compass sense of night-migratory songbirds using the information theory approach devised by Hiscock et al. (10). To avoid explicit modeling of more than a million receptor cells in the retina, neighboring cells have been grouped together on the basis that they should have a similar ever structures serve to align and immobilize it. It is therefore relevant to explore how $\varepsilon_{H}$ depends on the three parameters in Eq. 1.

Fig. 7, a–c show how $\varepsilon_{H}$ for orientation O1 depends on $a$, $b$, and $c$ in Eq. 1 for different total number of photons, $rp$. Relative to the default values, the heading error can be reduced by changing the offset away from 0.5 in either direction (Fig. 7 a), by increasing the amplitude of the signal (Fig. 7 b), and by reducing its width (Fig. 7 c). The dependence on the amplitude, $b$, is relatively simple; $\varepsilon_{H}$ is a function of $b^2rp$ only (Fig. S6). That is, if the amplitude of the signal is doubled, four times fewer photons in total are required to achieve the same $\varepsilon_{H}$. Under similar conditions, O2 and O3 exhibit the same kind of dependence on $a$, $b$, and $c$ but generally give smaller values of $\varepsilon_{H}$ (as noted above for the default signal).

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![Figure 7](image-url)
response to the geomagnetic field. This approximation has been validated here by the finding that the lower bound error, $\varepsilon_{\text{H}}$, is independent of the size of these groups provided the total number of photons absorbed in the retina, and therefore radical pairs formed, is fixed (Fig. 2). Doubling the number of groups and halving the number of photons absorbed by each group, for example, has no effect on $\varepsilon_{\text{H}}$. The only restrictions on this finding are that there must be at least 100 groups of cells distributed uniformly around the retina and that the parameters of the model signal in Eq. 1 should not have extreme values.

The conclusion that the total number of photons controls the precision of the compass also has a bearing on a question posed in (5): whether $\varepsilon_{\text{H}}$ would be affected by considering the night sky as a collection of bright stars on a dark background rather than a uniform source of dim light. The inference that can be drawn from the results presented here is that as long as one considers the same total photon flux, the compass performance should not change.

In their treatment, Hiscock et al. considered a single intracellular orientation of the magnetoreceptor proteins (O1), chosen for the simplicity of its visual modulation pattern (Fig. 4; (10)). In terms of $\varepsilon_{\text{H}}$, all other magnetoreceptor orientations perform better than O1 and, other things being equal, orientations O2 and O3 are close to optimal (Fig. 3). Given that essentially nothing is known about how cryptochromes might be immobilized and aligned in the retina, the choice of O1 can be seen as completely arbitrary. What our analysis has shown is that the precision of the compass bearing derived from a radical pair sensor can be optimized by adjusting the orientation of the receptor molecules within the cells.

Furthermore, by calculating individual lower bounds, $\varepsilon_{\text{H}}(\nu, \kappa)$, we have been able to shed light on why some receptor orientations are more successful than others and to show that by concentrating cells into the essential region for each orientation, the performance of the compass can be enhanced (Figs. 4, 5, and 6). It is not clear whether this finding has biological significance.

The angular precision of the information available from a radical pair compass sense depends on the quantum yield of the signaling state and how it varies with the direction of the geomagnetic field with respect to the aligned receptor proteins. We have modeled this dependence by means of Eq. 1 using default values of the parameters $a$, $b$, and $c$ that give an approximate match to a detailed spin dynamics simulation of the [FAD$^*$ TrpH$^+$] state of cryptochrome (10). Although a certain amount is known about the magnetic sensitivity of this radical pair from spectroscopic measurements on purified cryptochromes (16,17), there is no information on the anisotropy of the magnetic field effect in vivo. It is therefore possible, indeed likely, that the form of Eq. 1 that best describes the behavior in vivo will deviate significantly from the model used here. Figs. 7 and 8 and Table 2 show that there is considerable scope for optimizing $\varepsilon_{\text{H}}$ by making relatively modest changes to $a$, $b$, and $c$.

Previous spin dynamics simulations of the magnetic sensitivity of cryptochrome radical pairs have identified a number of ways in which this optimization could be realized. These include 1) a spin coherence lifetime longer than the 1 $\mu$s adopted here (36); 2) asymmetric recombination, i.e., different rate constants for the reactions of singlet and triplet radical pairs (37); 3) replacement of the TrpH$^+$ component of the radical pair by a radical with fewer and smaller electron-nuclear hyperfine interactions (19); and 4) modified reaction schemes involving paramagnetic scavengers (38,39). All of these factors have the potential to alter the offset, amplitude, and width of $\Phi_\text{S}(\zeta)$ and so reduce the expected error in the derived compass bearing. Conversely, the uncertainty in the head direction can be expected to increase if the amplitude of the signal in vivo is smaller than in the default model.

**SUPPORTING MATERIAL**

Supporting Material can be found online at https://doi.org/10.1016/j.bpj.2020.12.023.
AUTHOR CONTRIBUTIONS

P.J.H. conceived and designed the study. Y.R. performed the calculations with advice from H.G.H. All authors discussed the results and conclusions. Y.R. and P.J.H. wrote the manuscript.

ACKNOWLEDGMENTS

We are grateful for the following financial support: the Air Force Office of Scientific Research (Air Force Materiel Command, USAF award no. FA9550-14-1-0095), the European Research Council (under the European Union’s Horizon 2020 research and innovation programme, grant agreement no. 810002, Synergy Grant: QuantumBirds), and the Office of Naval Research Global, award no. N62909-19-1-2045.

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