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Radical pairs may play a role in microtubule reorganization

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The exact mechanism behind general anesthesia remains an open question in neuroscience. It has been proposed that anesthetics selectively prevent consciousness and memory via acting on microtubules (MTs). It is known that the magnetic field modulates MT organization. A recent study shows that a radical pair model can explain the isotope effect in xenon-induced anesthesia and predicts magnetic field effects on anesthetic potency. Further, reactive oxygen species are also implicated in MT stability and anesthesia. Based on a simple radical pair mechanism model and a simple mathematical model of MT organization, we show that magnetic fields can modulate spin dynamics of naturally occurring radical pairs in MT. We propose that the spin dynamics influence a rate in the reaction cycle, which translates into a change in the MT density. We can reproduce magnetic field effects on the MT concentration that have been observed. Our model also predicts additional effects at slightly higher fields. Our model further predicts that the effect of zinc on the MT density exhibits isotopic dependence. The findings of this work make a connection between microtubule-based and radical pair-based quantum theories of consciousness.

The question of how we perceive and experience the world we live in is a fascinating, long-standing open question in neuroscience, philosophy and psychology. This conscious experience vanishes during dreamless sleep or under general anesthesia^{1,2}. Every day millions of surgeries all over the world would not be possible without anesthetics. However, despite a century of research, the mechanisms by which anesthetics cause a reversible loss of consciousness remain obscure³. During anesthesia, old memories are preserved, but no new memory is formed. Furthermore, anesthetics act relatively selectively on consciousness, as many non-conscious brain activities, including sensory-evoked potentials, persist during anesthesia. Understanding anesthesia, apart from its benefits in designing and developing novel anesthetics, could help explain the mystery of consciousness.

The connections between theories of anesthesia, related to neural correlates of consciousness, and the Meyer Overton correlation–solubility of anesthetics in a non-polar, ‘hydrophobic’ medium—has not been completely understood, and direct anesthetic effects on synaptic receptors are variable and inconsistent. Further, single-cell organisms perform cognitive activities predominantly by cytoskeletal microtubules (MTs) and are inhibited by anesthetic gases even without synapses or networks⁴. Moreover, Linganna et al. reported that alteration of MT stability is one of a number of mechanisms of inhaled anesthetics related to the function⁵. Bernard showed that anesthetics act directly on cytoplasm, depending on cytoskeletal proteins’ dynamics comprising actin filaments and MTs⁶. Franks and Lieb found that anesthetics act directly within proteins in non-polar hydrophobic regions⁷. This led some anesthetic researchers to search for new target protein/molecule for anesthetics. Moreover, Eckenhoff et al. found that anesthetics bind to 23 membrane proteins and 34 cytoplasmic proteins, including actin and tubulin^{8,9}. Studies suggest anesthetics exert their effects via acting on protein reaction networks involved in neuronal growth, proliferation, division, and communication, which depend on MTs¹⁰. Although the affinity of anesthetics binding to tubulin is a thousand times weaker than to membrane protein, the abundance of tubulin is a thousand to ten thousand times more than membrane protein sites.

It has also been proposed that anesthetics act on quantum electronic activity in neuronal hydrophobic regions rather than binding to specific receptors. Consistently, Turin et al. showed that specific electron spin resonance (ESR) signals, consistent with free electrons, can be observed during anesthesia¹¹. The same authors proposed that the anesthetic action may involve some form of electron transfer. Moreover, Li et al. showed experimentally that isotopes of xenon with non-zero nuclear spin had reduced anesthetic potency in mice compared with isotopes with no nuclear spin¹². These findings are consistent with the idea that different nuclear spins of anesthetics can modulate the electron transfer process differently. Motivated by this line of thought, a recent study shows that radical pairs may explain the mechanism behind xenon-induced anesthesia¹³.

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Quantum physics has been proposed to be part of the solution for the mystery of consciousness. In particular the holistic character of quantum entanglement might provide an answer to the binding problem¹⁴. In the 1990s, Penrose and Hameroff proposed a theory of consciousness based on quantum computations in MTs^{15–18}. Computational modeling suggested that electron resonance transfer among aromatic amino acid tryptophan (Trp) rings in tubulin (subunits of MTs) in a quantum electronic process could play roles in consciousness¹⁹. Craddock et al. showed that anesthetic molecules might bind in the same regions and hence result in loss of consciousness²⁰. In a recent experiment, Zhang et al. observed a connection between electronic states and vibrational states in tubulin and MTs²¹. However, quantum electronic coherence beyond ultrafast timescales demands more supporting evidence and has been recently challenged experimentally²². In contrast, quantum spin coherence could be preserved for much longer timescales²³. For example, Fisher has proposed that phosphorus nuclear spins could be entangled in networks of Posner molecules, Ca₉(PO₄)₆, which could form the basis of a quantum mechanism for neural processing in the brain²⁴. However, this particular spin-based model also requires more supporting evidence and recently has faced experimental challenges²⁵.

It is known that magnetic fields (MFs) can influence different brain functions^{26–32}. Recently, it has been shown that shielding the geomagnetic field—exposure to hypomagnetic field (HMF)—influences adult hippocampal neurogenesis and hippocampus-dependent cognition in mice, where reactive oxygen species (ROS) are implicated³³. There exists a considerable amount of evidence showing that MFs affect MTs^{34–39}. Wang et al. show that exposure to HMF caused tubulin assembly disorder⁴⁰. Moreover, Wu et al. observe that low-frequency sub-millitesla MF modulates the density of MTs in cells⁴¹. All these observations establish the magnetosensitivity of MTs for wide ranges of MF strengths.

Magnetosensitive reactions often involve radical molecules—transient molecules with an odd number of electrons⁴². A radical pair is a short-lived reaction intermediate comprising two radicals formed in non-equilibrium states whose unpaired electron spins may be in a superposition of singlet (S) and triplet (T) states⁴³, depending on the parent molecule's spin configuration⁴⁴. The radical pair mechanism (RPM) is the most promising explanation for weak magnetic field effects on chemical reactivity⁴⁵. Schulten was the first to propose the RPM to explain the magnetoreception of migratory birds⁴⁶, and to date, the RPM is the most well-established model for this phenomenon⁴⁷. Recently, it has also been proposed that RPM may explain xenon induced general anesthesia¹³, lithium effects on hyperactivity⁴⁸ and the magnetic field effects on the circadian clock⁴⁹.

MTs are made of $\alpha - \beta$ tubulin heterodimers. The distribution and organization of MTs in cells are governed by a large number of MT-associated proteins (MAPs)⁵⁰. MTs play crucial roles in cell shape, cell transport, cell motility, cell division^{51–57}, neuronal polarity⁵⁸, information processing of living systems⁵⁹, synaptic activity⁶⁰, regulating the precise timing of nerve spikes⁶¹, and Alzheimer's disease (AD)⁶².

Evidence suggests that oxidative stress is vital for regulating actin and MT dynamics⁶³. MTs contain specific amino acid residues, including Trp, tyrosine (Tyr), and phenylalanine (Phe), susceptible to oxidation. This, in turn, affects the ability of MT to polymerize and causes the severing of actin microfilaments in neuronal and non-neuronal cells. Contrarily, ROS inhibition causes aberrations in actin polymerization, decreases neurite outgrowth, and affects neurons' normal development and polarization.

To be magnetically sensitive, tubulin must have (para)magnetic agents. With an unpaired electron, radicals are paramagnetic and could serve as magneto-sensing molecules. Trp and O₂^{•-} radicals are well-known radicals, particularly in animal avian magnetoreception, in the form of [Trp^{•+} . . . FAD^{•-}] or [FADH[•] . . . O₂^{•-}], wherein the latter case FADH[•] is the donor and O₂^{•-} acceptor while in the former case Trp^{•+} is the donor and FAD^{•-} is the acceptor^{45,47,64,65}. It is thought that [Trp^{•+} . . . FAD^{•-}] is formed in a photo-induced process. This case is similar to the NMDA receptor (NMDAR) in Xenon-induced anesthesia¹³. In both tubulin and the NMDAR, Trp is one of the key aromatic molecules^{66,67}. It is also known that Trp can absorb environmental photons to reach an excited state, and it is considered in the excitation coherency in tubulins⁶⁸. Furthermore, it is shown that Trp and superoxide can be involved in an electron transfer process^{69,70}. For instance, in the context of the bird's magnetic compass, a new study suggests that involvement of other radicals rather than the conventional ones is plausible⁷¹. Moreover, this model could be adapted for other RP complexes in the microtubule dynamics, e.g. involving flavin and Tyr. Such radical pairs can be formed via flavoenzymes^{72,73}.

Various studies have proposed mathematical models for the dynamics and stability of MTs^{74,75}. Craddock et al. show that the dynamics of MT can be framed in a simple kinetic model⁷⁶. In the context of the RPM, Player et al. show that quantum effects can be introduced to a kinetic model by considering the quantum effects on the corresponding reaction rates in the chemical equations⁷⁷. Taking the same approach, a new study shows that quantum effects can directly modulate the period of the circadian clock in *Drosophila*, where the spin dynamics of the RPs are the key elements⁴⁹.

In the present work, we propose that there are naturally occurring RPs in the form of TrpH^{•+} and O₂^{•-}, which is an important paramagnetic ROS, that play important roles in MT organization, as shown in Fig. 1. Oxygen is abundant, and tryptophan is an essential aromatic ring for tubulin; thus, the formation of such radical pairs can occur broadly. Our model predicts that the applied magnetic fields alter the spin dynamics of such RPs, similar to Ref.¹³, and hence modulate the assembly of MTs in cytoskeleton. It is also known that changes in zinc ion concentration in neurons influence the stability of polymerized MTs⁷⁶. Following the work of Craddock et al.⁷⁶, our model further predicts that the effect of zinc on the MT density exhibits isotopic dependence.

In the following, we review the experimental results for the effects of applied magnetic field^{40,41} on the density of MTs. We then describe the quantum spin dynamics of our radical pair model and a simple kinetic model for the MT dynamics. Next, we introduce the quantum effect to the density of the MT, and we show that our model can reproduce the observed magnetic field effects; it further makes new predictions for experiments using low-frequency MFs. Lastly, the model predicts that the zinc effect on the MT density is isotope dependent.

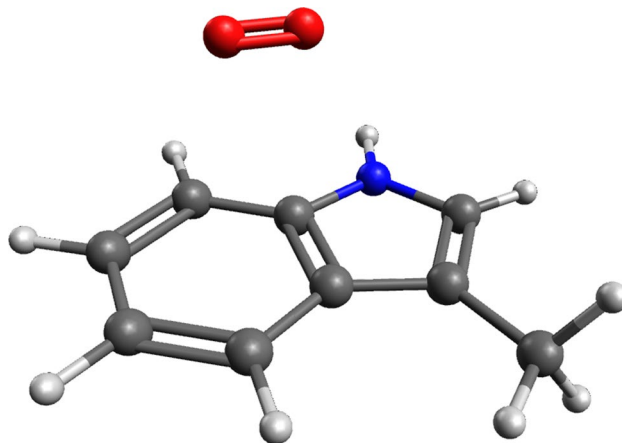


Figure 1. Schematic presentation of TrpH^+ [the aromatic molecule] and O_2^- [the red molecule] radical pair, considered in the RPM model in the present work, similar to Ref.¹³. The radical pair undergoes interconversion between singlet and triplet states. Image rendered using Avogadro (<https://avogadro.cc>).

Results

Prior experiment. Wang et al. report that shielding Earth's geomagnetic field (GMF) (0.025–0.065 mT) caused disorders in tubulin self-assembly⁴⁰. They show that the absorbance at 350 nm, which is for monitoring tubulin self-assembly, was altered by exposure to 30 min HMF. Average gray volume per cell was reported based on the amount of fluorescence in each cell. About 95% of tubulin were assembled in the GMF, while much less of the tubulin assembled ($\sim 64\%$) in the HMF. In that work, the magnitude of the residual GMF was 10–100 nT.

Radical pair model calculations. We develop an RP model to reproduce the HMF effects on the MT density observed by Wang et al.⁴⁰. Among the amino acids in MTs, as mentioned above, Trp is redox active⁷⁰, as shown by its involvement in RP formation in the context of cryptochrome, and could feasibly participate in the creation of RPs. We propose that the magnetic field interacts with the spins of RPs on Trp and superoxide. Note, that superoxide is thought to form RPs with flavins in other contexts⁷⁸. The correlated spins of RP are assumed to be in the $[\text{TrpH}^+ \dots \text{O}_2^-]$ form, following Ref.¹³, where the unpaired electron on each molecule couples to the nuclear spins in the corresponding molecule. Oxygen has zero nuclear spin and thus zero coupling with its nucleus.

We consider a simplified system in which the unpaired electron on TrpH^+ is coupled to the Trp's β -proton with the largest isotropic HF coupling constant (HFCC) of 1.6046 mT⁷⁹ among all the nuclei in Trp. We consider only Zeeman and HF interactions^{45,80}. For the RPs, we assume the g -values of a free electron (which is an excellent approximation in the low-field regime that we are considering here). The Hamiltonian for the RP system reads:

$$\hat{H} = \omega \hat{S}_{A_z} + a_A \hat{S}_A \cdot \hat{I}_1 + \omega \hat{S}_{B_z}, \quad (1)$$

where \hat{S}_A and \hat{S}_B are the spin operators of radical electron on TrpH^+ and O_2^- , respectively, \hat{I}_A is the nuclear spin operator of TrpH^+ 's β -proton, a_A is HFCC, and ω is the Larmor precession frequency of the electrons due to the Zeeman effect. In the model presented here, for zinc effects, a_B corresponds to the nuclear spin of zinc. We assumed the initial state of RPs to be singlet states (see the “Discussion” section).

The spin density matrix of RPs can be calculated using the Haberkorn master equation, where the kinetic reaction rates for singlet and triplet products are assumed to be equal^{43,81,82}. For simplicity, the kinetic reaction rates were assigned equal first-order rate constants, k . Introducing spin relaxation phenomenologically^{83,84}, the fractional triplet yield can be calculated as:

$$\Phi_T = \frac{3}{4} + \frac{k}{4(k+r)} - \frac{1}{M} \sum_{m=1}^{4M} \sum_{n=1}^{4M} |\langle m | \hat{P}^S | n \rangle|^2 \frac{k(k+r)}{(k+r)^2 + (\omega_m - \omega_n)^2}, \quad (2)$$

where M is the nuclear spin multiplicity, \hat{P}^S is the singlet projection operator, $|m\rangle$ and $|n\rangle$ are eigenstates of \hat{H} with corresponding eigenenergies of ω_m and ω_n , respectively, k is the RP reaction rate, and r is the RP spin-coherence rate (relaxation rate). In this model, we assumed the reaction rates for singlet and triplet have the same values. Of note, the singlet and triplet product of the RP system in $[\text{TrpH}^+ \dots \text{O}_2^-]$ are H_2O_2 and $\text{O}_2^{\cdot-}$ ⁷⁸, respectively, which are the major ROS in redox regulation of biological activities and signaling⁸⁵.

Here we look at the dependence of the triplet yield on changes in the strength of the external static magnetic field for the $[\text{TrpH}^+ \dots \text{O}_2^-]$ radical complex, as shown in Fig. 2, for $k = 10^6 \text{ s}^{-1}$, and $r = 10^5 \text{ s}^{-1}$ with $a_A = 1.6046 \text{ mT}$. One can notice a fairly strong HMF effect (the triplet yield goes from around 60% to around 40%). Our choices for the rate constants are discussed below and in the “Discussion” section.

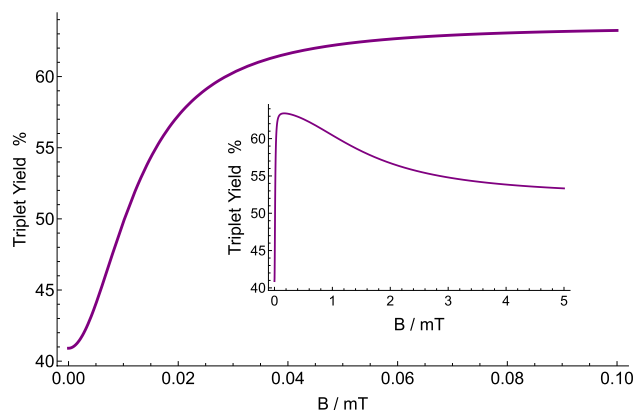


Figure 2. The dependence of the triplet yield of the $[\text{TrpH}^+ \dots \text{O}_2^-]$ complex on applied static magnetic field for $r = 10^5 \text{ s}^{-1}$, $k = 10^6 \text{ s}^{-1}$, $a_A = 1.6046 \text{ mT}$. The triplet yield goes from around 60% to around 40% by changing the magnetic field strength from GMF to HMF. The strong HMF effect is further emphasized by the inset.

Chemical kinetics model for MT dynamics. We use a simple mathematical model for the dynamics of MT, following the work of Craddock et al.⁷⁶. This model is based on the interconversion of the free tubulins, Tu, and the MT in cytoskeleton:



where k_p and k_d are the polymerization rate and the depolymerization rate, respectively. The chemical equation reads as follows:

$$\frac{[d\text{MT}(t)]}{dt} = k_p[\text{Tu}(t)] - k_d[\text{MT}(t)], \quad (4)$$

which yields $[\text{MT}(t)] = \frac{k_p[\text{P}]}{k_p + k_d} (1 - e^{-(k_p + k_d)t})$.

Craddock et al. suggest that changes in the concentration of zinc can be incorporated by modulating the polymerization rate⁷⁶. In the present work, it is assumed that the total tubulin protein concentration $[\text{P}]$ is $400 \mu\text{M}$, such that $[\text{MT}] + [\text{Tu}] = [\text{P}]$, $k_p = 90 \text{ s}^{-1}$ and $k_d = 150 \text{ s}^{-1}$. These values are chosen such that we could be able to reproduce the experimental findings, which are comparable to those in Ref.⁷⁶.

Quantum effects on microtubule density. Here we explain how quantum effects can play an essential role in tubulin polymerization.

Spin is a magnetic moment and hence obeys the spin conservation. This leads to spin selectivity of chemical reactions. In other words, depending on whether radical pairs are in a singlet or triplet state, the chemical reaction will take different paths. It thus results in modulating the reaction rates. The work of Wang et al.⁴⁰ shows that the absence of the GMF decreased the tubulin polymerization. Thus, it is natural to assume that effects of applied magnetic fields and hyperfine interactions can be incorporated into the classical model Eq. (4) by influencing the polymerization rate, k_p , similar to other studies for introducing zinc effect into the stability of polymerized MTs⁷⁶. The key assumption in our model is that this rate is influenced by a RP reaction. The effect of the triplet yield change on k_p reads:

$$k'_p \propto k_p \frac{\Phi'_T}{\Phi_T}, \quad (5)$$

where k'_p , Φ_T , and Φ'_T are the modified rate constant k_p , the triplet yield under natural quantum effects (only GMF and no isotope effects), and the triplet yield resulting from quantum effects due to the external MF effects and hyperfine interactions from isotope effects, respectively.

Magnetic field effects on microtubule density. Here, we look at the explicit effects of an applied magnetic field on the density of microtubules. Using Eq. (4), we explore the parameter space of relaxation rate r and recombination rate k in order to investigate the effects of shielding geomagnetic field on MT's density. Wang et al. report that the ratio MT density of geomagnetic field over hypomagnetic field is about 1.48⁴⁰. Figure 3 show that the ratio of the MT density of GMF over HMF can reach above 1.3, which has the right trend compared to the experimental findings. However the uncertainty of the experiment was not reported. Our model predicts a magnetic dependence of the MT density. Figure 4 show the dependence of the MT density ratio of in GMF compared to applied static magnetic field, for $a_A = 1.6046 \text{ mT}$ based the RP complex of $[\text{TrpH}^+ \dots \text{O}_2^-]$, $k = 10^6 \text{ s}^{-1}$, and $r = 10^5 \text{ s}^{-1}$. Figure 4 indicates that exposure to static magnetic fields stronger than the geomagnetic field could

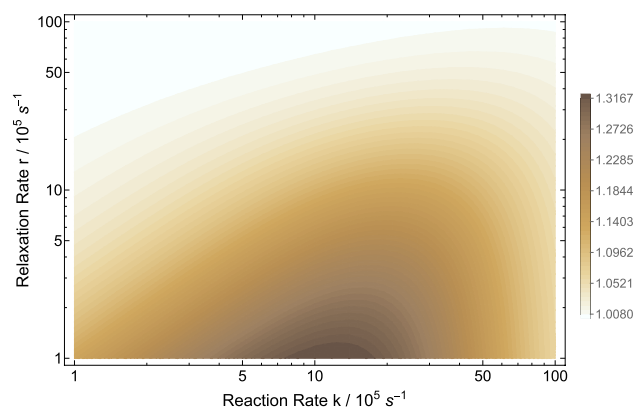


Figure 3. The RPM model prediction of the microtubule density ratio in geomagnetic field compared to hypomagnetic field based on the RP complex of $[\text{TrpH}^+ \dots \text{O}_2^-]$. The geomagnetic field and hypomagnetic field are 0.05 mT and 10 nT, respectively. The magnetic field modulates rate k_p for $a_A = 1.6046$ mT. The maximum HMF effect is obtained for $k \in [7 \times 10^5, 11 \times 10^5] \text{s}^{-1}$ and $r \in [10^5, 2 \times 10^5] \text{s}^{-1}$.

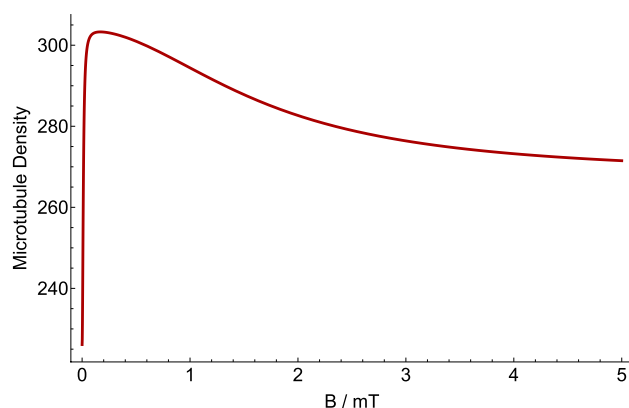


Figure 4. The dependence of the microtubule density ratio in geomagnetic field compared to applied static magnetic field based on the RP complex of $[\text{TrpH}^+ \dots \text{O}_2^-]$. The geomagnetic field is 0.05 mT. The magnetic field modulates rate k_p for $a_A = 1.6046$ mT, $r = 10^5 \text{s}^{-1}$, and $k = 10^6 \text{s}^{-1}$. HMF causes strong decrease on the microtubule density. The maximum microtubule density occurs around GMF.

decrease the the microtubule density ratio. The maximum MT density occurs around 0.05 mT, which is in the range of the GMF.

Zinc isotope effect on microtubule density. The RPM typically leads to isotope effects^{13,48}, and thus an isotope effect would be a good test of our proposal. It is known that alterations in zinc ion concentration in neurons influence the stability of polymerized MTs⁷⁶. Zn is a positively charged ion. Thus it is natural to assume that Zn^{2+} couples with a molecule with a negative charge. Among all stable isotopes of zinc, only ^{67}Zn has a nuclear spin of $I_B = -\frac{5}{2}$, with a natural abundance of 4%. Here we explore the isotope effect of zinc on the density of MTs. In this model nuclear spin of zinc modulates the spin dynamics of the RPs via hyperfine interactions. The Hamiltonian for the RP system here reads:

$$\hat{H} = \omega \hat{S}_{A_z} + a_A \hat{S}_A \cdot \hat{I}_1 + \omega \hat{S}_{B_z} + a_B \hat{S}_B \cdot \hat{I}_2, \quad (6)$$

where \hat{I}_2 is the nuclear spin operator of Zn^{+2} , and $a_B = -11.39$ mT is the HFCC of Zn^{+2} .

We look at the effect of ^{67}Zn on the MT density. We assume that ^{67}Zn interacts with the superoxide radical. Our model predicts that administration of ^{67}Zn increases the density of MTs compared to Zn with zero nuclear spin, as shown in Fig. 5. We explored the parameter space of relaxation rate r and recombination rate k in order to investigate the effects of the ^{67}Zn treatment on MT's density, for $a_A = 1.6046$ mT and $a_B = -11.39$ mT, as shown in Fig. 5. Figure 6 shows the dependence of the MT density ratio of the administration of Zn over ^{67}Zn on the strength of applied magnetic field based on the RP complex of $[\text{TrpH}^+ \dots \text{O}_2^-]$. The geomagnetic field is 0.05 mT. The magnetic field modulates rates k_d and k_p for $r = 10^5 \text{s}^{-1}$ and $k = 10^6 \text{s}^{-1}$. Our model predicts that administering ^{67}Zn increases the MT density compared to Zn without nuclear spin.

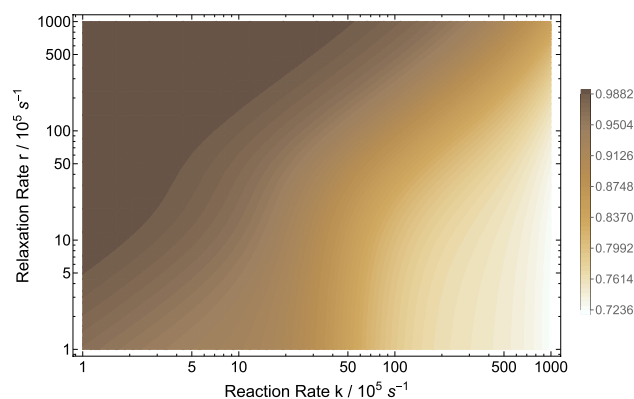


Figure 5. The RPM model prediction of the MT density ratio of the administration of Zn (with zero nuclear spin) over ^{67}Zn (with nuclear spin of $I_B = -\frac{5}{2}$) based on the RP complex of $[\text{TrpH}^+ \dots \text{O}_2^-]$. ^{67}Zn The geomagnetic field has a strength of 0.05 mT. ^{67}Zn 's nuclear spin modulates rate k_p for $a_A = 1.6046$ mT and $a_B = -11.39$ mT.

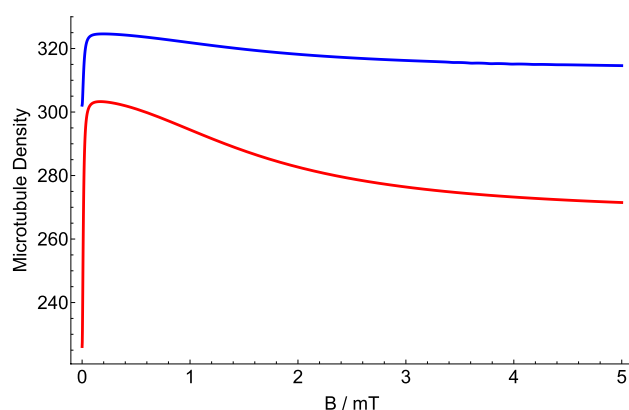


Figure 6. The dependence of the MT density of the administration of Zn (with zero nuclear spin) [Red] and ^{67}Zn (with nuclear spin of $I_B = -\frac{5}{2}$) [Blue] on the strength of applied magnetic field based on the RP complex of $[\text{TrpH}^+ \dots \text{O}_2^-]$. The geomagnetic field is 0.05 mT. The magnetic field modulates rate k_p for $a_A = 1.6046$ mT, $a_B = -11.39$ mT, $r = 10^5 \text{ s}^{-1}$, and $k = 10^6 \text{ s}^{-1}$.

Atom	Charge population	Spin population
O	-0.203235	0.554431
O	-0.203243	0.554413
Zn	1.406478	-0.108844
Sum	1	1

Table 1. Mulliken charge and spin population of $[\text{Zn}^{2+} \dots \text{O}_2^-]$.

DFT analysis. The ORCA package⁸⁶ was used for our $\text{Zn}^{2+}\text{-O}_2^-$ DFT calculations, and the molecular structure was optimized using PBE0/def2-TZVP. The orbitals obtained from the optimization calculations were used to calculate orbital energies as well as the hyperfine coupling constant a_B . Using RI-B2GP-PLYP/def2-QZVPP⁸⁷, we obtained $a_2 = -11.39$ mT. In these calculations, relativistic effects were treated by a scalar relativistic Hamiltonian using the zeroth-order regular approximation (ZORA)⁸⁸. Solvent effects were considered by using the conductor-like polarizable continuum model (CPCM)⁸⁹, with a dielectric constant of 2. The resulting Mulliken charge and spin population of the $[\text{Zn}^{2+}\text{-O}_2^-]$ complex indicates that the unpaired electron resides primarily on the O2 molecule but is extended slightly onto the zinc atom, see Table 1. The highest occupied molecular orbital (HOMO) of $[\text{Zn}^{2+}\text{-O}_2^-]$ is shown in Fig. 7.

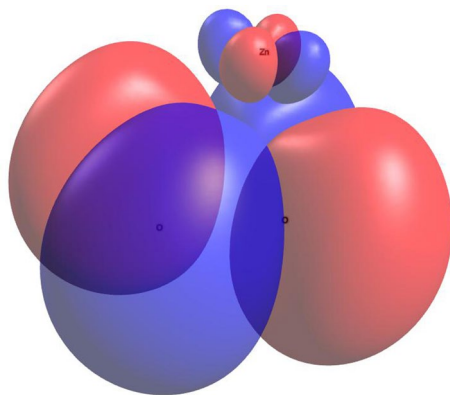


Figure 7. The highest occupied molecular orbital of $\text{Zn}^{2+}\text{-O}_2^-$. Imaged rendered using Avogadro (<https://avogadro.cc>).

Discussion

In the present work, our main goal was to explore whether an RP model can help explain the magnetic field effects on the MT density. We showed that the quantum effects influence the rates in the chemical kinetics of the MT dynamics, and then this results in a change in the density of MT in cytoskeleton. Our model reproduces the experimental findings of Ref.⁴⁰ fairly well, as shown in Fig. 3. Our model further predicts that exposure to static magnetic fields stronger than the geomagnetic field could decrease the microtubule density ratio, with the maximum microtubule density occurs at a magnetic field strength in the range of the geomagnetic field, which might have evolutionary roots.

The O_2^- radical is thought to have a fast spin relaxation rate. However, it has also been proposed that this fast spin relaxation can be decreased by reducing the molecular symmetry in the biological environment^{64,90–92}, i.e. an asymmetric environment. In this case the degeneracy of the HOMOs (π_g) of O_2^- will be removed and hence its fast reorientation molecular will be prevented. It is shown experimentally that in frozen solutions⁹³ and alkali halide crystals⁹⁴ such the fast spin relaxation of O_2^- can be hindered. Additionally, Kattnig and Hore show that scavenger species around the superoxide radical can also reduce its fast spin relaxation^{95,96}.

The present work predicts that the zinc effects on the MT density exhibits an isotope dependent manner. Isotope effects are generally a good indication for radical pairs. In addition, magnesium (Mg) is required for MT stability and function^{97–99}. Furthermore, Buchachenko et al. showed that adenosine triphosphate (ATP) production was more than two folds in the presence of ^{25}Mg compared to ^{24}Mg in purified pig skeletal muscle PGK¹⁰⁰. Hence, it would be interesting to perform an experiment to probe Mg isotope effects in MT stability.

The ground state of the oxygen molecule is a triplet state. For this reason, oxygen-based radical pairs are often assumed to start from triplet states. However, if the dioxygen molecule goes to its singlet state, the initial state of the radical pairs will be a singlet state. Singlet oxygen is generated naturally^{101,104–106} and therefore there is also the possibility of the pair being created from singlet oxygen. In this case, the initial state of the radical pairs will be singlet states. Furthermore, spin-orbit interactions lead to the non-radiative transition between two electronic states with different spin multiplicity (e.g. singlet and triplet)– intersystem crossing (ISC), which is ubiquitous and important in fields ranging from chemical physics to chemical biology, including chiral molecules^{70,107–111}.

A well-known indication of the pathogenesis of tauopathy–loss-of-function effects on the microtubules and the gain-of-function effects of the toxic tau species-is oxidative stress, which contributes to tau phosphorylation and the formation of neurofibrillary tangles¹¹². However, the mechanisms behind the connection between reactive oxygen species (ROS) generated by oxidative stress and tau hyperphosphorylation are elusive⁶⁸. Further, redox signaling and oxidative stress regulate cytoskeletal dynamics⁶³. Proper balances between chemical reduction and oxidation (known as redox balance) are crucial for normal cellular physiology. Imbalances in the production of oxidative species lead to DNA damage, lipid peroxidation, and aberrant post-translational modification of proteins, which could induce injury, cell death, and disease⁸⁵. These findings further emphasize the role of radicals and likely the need for a RPM in the context of the brain. Our proposed RPM model for magnetic field effects and Zn isotope effects on the microtubule organization includes superoxide radical.

It is also worth mentioning that any changes in the natural system could lead to various effects and complexify the entire system. Nonetheless, changes in superoxide concentration would likely affect the polymerization rate. This is in line with other observations in the work of Zhang and colleagues, where they reported that exposure to hypomagnetic fields caused hippocampal neurogenesis in mice to hypomagnetic fields caused hippocampal neurogenesis in mice³³, however, this adverse effect was reversible by elevating ROS levels through pharmacological inhibition of ROS removal. Thus, it would be interesting to test whether modulating ROS levels pharmacologically can influence the HMF effects on tubulin polymerization.

Microtubules not only play crucial roles in cell shape, cell transport, cell motility, and cell division, but also are important targets for curing devastating diseases, such as Alzheimer's disease^{113–115}, Parkinson's diseases^{116,117}, and cancer^{118–120}. The dynamics of MAPs signaling proteins play critical roles in the MT network, hence in the process of synaptic plasticity and brain function. Studies suggest that memory is encoded in MT of neuronal

dendrites and cell bodies. Anesthetic causes loss of consciousness and memory formation via acting on MTs^{121–123}. Disintegration and separation of the MT-associated protein tau have been observed in memory neurodegenerative diseases and disorders, e.g., in AD¹²⁴; MT-stabilizers are currently the target for curing such diseases^{62,125,126}. However, the underlying mechanism for such diseases is mostly unknown. Thus this project also paves a potential path to study other functionalities of the body and the brain connected to MTs in the light of the RPM.

In conclusion, our results suggest that quantum effects may underlie the magnetic field effects on the microtubule dynamics. This is likely a similar mechanism to those behind magnetoreception in animals⁴⁷, xenon-induced general anesthesia¹³, lithium treatment for mania⁴⁸, the magnetic field effects on the circadian clock⁴⁹. Our work is thus another piece of evidence that quantum entanglement^{14,24,127–134} may play essential roles in the brain's functions, anesthesia, and consciousness^{15,135}. Particularly, the photo-emission of singlet oxygen could serve as quantum messengers to establish long-distance connections¹³⁶ that might be essential for consciousness. Our work also provides a potential connection between microtubule-based and spin-based quantum approaches to consciousness.

Data availability

The generated datasets and computational analysis are available from the corresponding author on reasonable request.

Received: 28 September 2021; Accepted: 1 April 2022

Published online: 12 April 2022

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Acknowledgements

The authors would like to thank Jack Tuszyński for valuable discussions. This work was supported by the Natural Sciences and Engineering Research Council of Canada.

Author contributions

H.Z.H. and C.S. conceived the project; H.Z.H. performed the calculations; H.Z.H. and C.S. wrote the paper; C.S. supervised the project.

Competing Interests

The authors declare no competing interests.

Additional information

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