A Possible Inductive Mechanism for Magnetogenetics

Dr. Michael G. Christiansen,[1,*] William Hornslien,[2] Prof. Simone Schuerle[1,*]

1 ETH Zürich, Department of Health Sciences and Technology

2 Norwegian University of Science and Technology, Department of Mathematical Sciences

* Authors to whom correspondence should be addressed: <michael.christiansen@hest.ethz.ch> and <simone.schuerle@hest.ethz.ch>

Abstract

Reports of genetically conferred sensitivity to magnetic stimuli have preceded plausible mechanistic explanations. Frequently, these experiments rely on a fusion of ferritin with a transient receptor potential vanniloid channel protein, speculating associated mechanical or thermal cues. However, it has been argued compellingly that the small magnetic moment of ferritin precludes these possibilities. Here, we offer an alternative hypothesis based on stochastic resonance that does not require appreciable interaction of ferritin with the applied field. Rather, we suggest that ferritin might act merely as a localized source of high frequency inductive noise on the membrane. When combined with externally applied time-varying fields, this noise might help surmount the activation threshold of endogenous voltage-gated ion channels. To explore this concept, we use the stochastic Landau-Lifshitz-Gilbert equation to model magnetization dynamics and compare the magnetic field noise resulting from ferritin and from a 15 nm magnetite particle.

Introduction

The broadly recognized usefulness of optogenetics and chemogenetics for enabling targeted actuation of neurons has spurred interest in development of an analogous "magnetogenetic" technique. Triggering activity via wireless, invisible, and facile magnetic stimuli in transfected neuronal subpopulations holds obvious appeal, and reports describing conferred sensitivity to magnetic fields have already appeared (Stanley et al., 2012; Stanley et al., 2016; Stanley, Sauer, Kane, Dordick, & Friedman, 2015; Wheeler et al., 2016). These studies typically incorporate one or more units of the iron storage protein ferritin into a transient receptor potential vanniloid (TRPV) channel protein. Because the TRPV family is known to trigger calcium influx in response to mechanical and thermal cues, magnetic interactions with ferritin have been presumed to be a source of similar effects (Barbic, 2019). However, cogent critique has cast doubt on these speculated mechanisms (Meister, 2016). The interaction of ferritin with attainable magnetic fields is far too weak for mechanical actuation, hysteresis heating of ferritin is demonstrably negligible, and even if extraordinary heat flow were to occur, local temperature increase is not expected (Anikeeva & Jasanoff, 2016; Davis et al., 2020; Keblinski, Cahill, Bodapati, Sullivan, & Taton, 2006). With an identified and tested mechanism, magnetogenetics could become a tool that can be used confidently and further optimized.

To help bridge this explanatory gap, here we suggest a potential mechanism applicable to excitable cell types expressing voltage gated ion channels. It accounts for actuation with inductively coupled stochastic resonance, mediated by ferritin localized on the cell membrane. Counterintuitively, ferritin may actually be better suited to this purpose than larger magnetite particles. To show this, we consider how the interaction of ferritin with a neighboring voltage-gated ion channel, in combination with a time-varying magnetic field, could plausibly serve to open these channels. We identify experiments that could test this hypothesis and consider possible implications if it were found to be valid.

Results and Discussion

Inductively Coupled Stochastic Resonance

A realistic model of ferritin is an essential starting point for any plausible mechanistic explanation of magnetogenetics. Historically, both the reported magnetic properties of ferritin and their interpretations have varied considerably, depending on their biological source and sample preparation. Nevertheless, magnetic characterization of ferritin spans nearly eight decades and can at least inform reasonable bounds for expected behavior (Michaelis, Coryell, & Granick, 1943). Ferritin consists of a protein shell with an outer diameter of approximately 12 nm that surrounds a biomineralized core with diameter 5.5 to 6.0 nm in humans, ranging up to about 8 nm in mollusks (Chasteen & Harrison, 1999). The size and crystallinity of human ferritin is comparable to ferritin derived from horse spleens, which is often studied. The core consists primarily of ferrihydrite with an approximate stoichiometry

$5Fe_2O_3 \cdot 9H_2O$, possibly incorporating trace phosphate impurities (Jutz, van Rijn, Santos Miranda, & Böker, 2015). Whether attributable to uncompensated antiferromagnetically ordered spins or the existence of multiple phases (Cowley, Janney, Gerkin, & Buseck, 2000), multiple empirical sources contend that ferritin's ferrihydrite core is superparamagnetic at physiological temperatures with a weak magnetic moment of approximately 300 μ_B (Brooks, Vymazal, Goldfarb, Bulte, & Aisen, 1998; Kilcoyne & Cywinski, 1995; Makhlouf, Parker, & Berkowitz, 1997). Experimental evidence for both an influence on T2 relaxation and feasibility of magnetic cell separation for bacteria expressing ferritin offer support for applying this interpretation to transgenically expressed ferritin (Liu et al., 2016; Matsumoto, Chen, Anikeeva, & Jasanoff, 2015).

In the hypothesis offered here, we suggest a mechanistic role for this superparamagnetism that shifts focus away from the thermal and mechanical sensitivities that have dominated the discussion and instead consider interaction with voltage gated ion channels (**Figure 1a**). Although voltage responsiveness has been observed in the TRPV family, interaction with endogenous ion channels gated at lower voltages could be more relevant (Nilius et al., 2005). A recent response from Wheeler et al. stated that a high density of expressed magnetogenetic membrane channels is required to reproduce their experimental results (Wheeler, Deppmann, Patel, & Güler, 2019). While this might be interpreted to reflect a low likelihood of an individual channel opening in response to magnetic stimulation, it would also be consistent with a proximity-based effect, in which the increased chances of adjacent ferritin on the membrane contributes to the mechanism. As the density of expressed proteins increases, even relatively rare or transient situations such as a ferritin sitting directly adjacent to a voltage-gated ion channel can be reasonably considered (**Figure 1a**).

Approximating the moment of ferritin as a 300 μ_B point dipole, the expected field magnitude at its surface is only a few mT and drops to a magnitude comparable to the geomagnetic field within 25 nm (**Figure 1b**). Assuming a voltage-gated ion channel with approximately 10 nm diameter, a ferritin directly adjacent to it should produce at most a small field of about 0.4 mT in the center of the channel. While this field magnitude is minute, inductive effects are determined by dB/dt, and the timescale of fluctuation of the moment plays a role of equal importance in determining this quantity. Individual superparamagnetic fluctuation of magnetic moments between preferred axes at a timescale kinetically limited by their anisotropy barrier is a well studied and directly observed phenomenon (Wernsdorfer et al., 1997). The temperature dependence of the timescale of stochastic reversal τ can be described in terms of an attempt rate τ_0, an intrinsic energy barrier U_B, the Boltzmann constant k_B, and the absolute temperature T (Néel, 1949):

$$\tau = \tau_0 \, Exp\left(\frac{U_B}{k_B T}\right). \quad (1)$$

The key relevant input quantities, τ_0 and U_B, can be estimated from data collected on various ferritin preparations. In the interest of putting the proposed mechanism on firmer footing, values can be selected

from a reasonable range that tend to bound or mitigate the relevant effects. τ_0 for superparamagnetic particles typically ranges from 100 fs to 1 ns (Kilcoyne & Cywinski, 1995), and although values on the order of 1 to 10 ps have been fitted for ferritin (Dickson et al., 1993; Kilcoyne & Cywinski, 1995), here we conservatively take 1 ns. Reported blocking temperatures seem to depend on preparation and characterization method. Although a blocking temperature of about 12 K seems most likely and is consistent with low temperature magnetization measurements (Dickson et al., 1993; Kilcoyne & Cywinski, 1995; Makhlouf et al., 1997), we have assumed the higher reported value of 40 K because increased anisotropy should also tend to mitigate the hypothesized effect (Chasteen & Harrison, 1999).

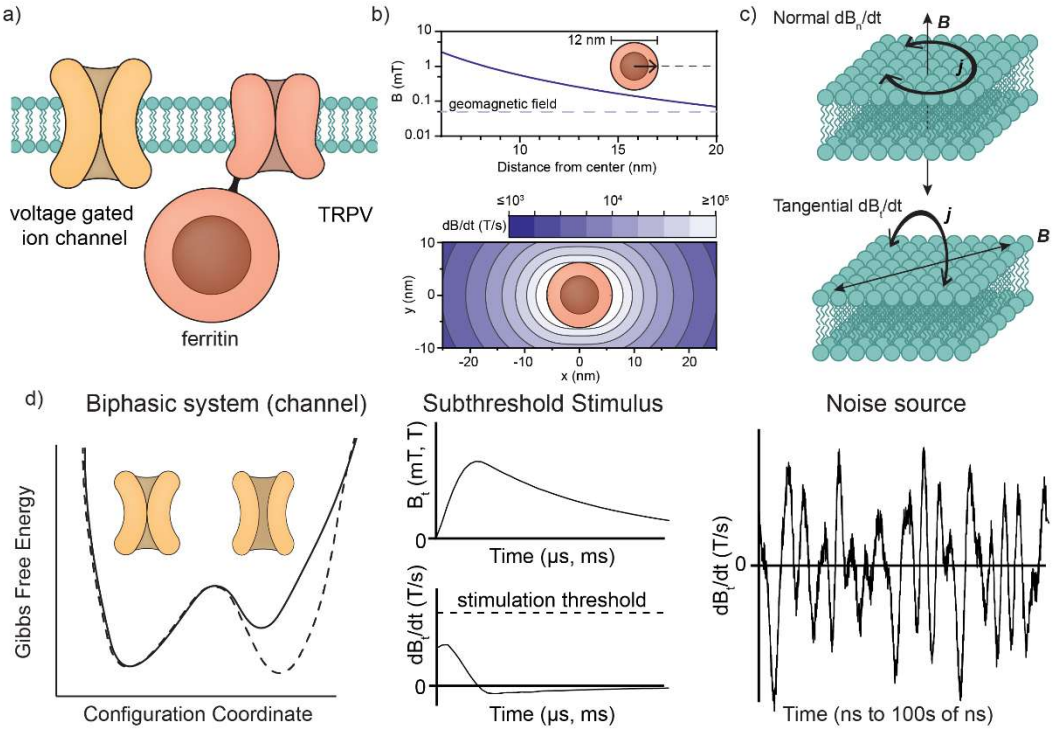

Figure 1. Conceptual illustrations. **a)** A transgenic TRPV channel protein incorporating a ferritin unit is expressed in the membrane, perhaps occurring near to any one of a variety of voltage-gated ion channels endogenously present in excitable cells. **b)** At top, the expected field magnitude versus distance is shown assuming a moment of 300 μB for ferritin. At bottom, the rate of change of the field is mapped for a macrospin model with conservative assumptions for kinetically limited reversal. **c)** A schematic illustrates why the component of the field changing tangentially to the membrane is most relevant to transmembrane potentials. **d)** The components that might enable inductively coupled stochastic resonance are represented pictorially. At left, the voltage gated ion channel represents a biphasic system that responds to applied potentials, including those induced by time varying fields. In center, a subthreshold stimulus is provided by an externally applied time-varying field. At right, noise is supplied by the fluctuation or precession of one or more ferritin magnetic moments.

As shown in the supplementary materials, these assumptions bound the fluctuation of ferritin to a characteristic timescale of about 20 ns. Time variation in magnetic flux on the channel occurring tangentially to the membrane would induce transmembrane voltage noise (**Figure 1c**). Estimating the order of magnitude of this dB/dt noise at the center of the ion channel, we find:

$$\frac{dB}{dt} \approx \frac{\Delta B}{\Delta \tau} = \frac{2(0.0004\ \mathrm{T})}{2 \times 10^{-8}\mathrm{s}} = 4 \times 10^{4}\ \mathrm{T\ s^{-1}}. \quad (2)$$

This bound for dB/dt in the local vicinity of the channel is comparable to empirically determined thresholds for inductive stimulation of neurons, reported to be about $2 \times 10^{3}\ \mathrm{T\ s^{-1}}$(McRobbie & Foster, 1984). The high frequency and limited spatial extent of this noise ensure that alone it should not produce spontaneous stimulation. Rather, the presence of one or more ferritins could merely act as a source of localized inductive noise on the membrane and ion channels.

This situation is altered by introducing a time varying magnetic stimulus acting on a timescale relevant to the channel dynamics, perhaps ranging from 10s of μs to 100s of ms. In their recent response to a failed replication study, Wheeler et al. stress the necessity for a *time varying* magnetic stimulus for reproducing their results (Wheeler et al., 2019). Similarly, other reports involving ferritin fused to TRPV often employ alternating magnetic fields in the 100s of kHz (Stanley et al., 2012; Stanley et al., 2015). Time-varying fields can elicit widespread induced voltages on the membranes of exposed neurons, a principle relied upon for transcranial magnetic stimulation (Romero, Davare, Armendariz, & Janssen, 2019). In the absence of magnetogenetic expression, these voltages are likely to be well below the necessary threshold to trigger an action potential.

With a nearby ferritin, however, a stochastic resonance phenomenon might emerge that accounts for the opening of the channel (McDonnell & Abbott, 2009; McNamara & Wiesenfeld, 1989). The necessary components are present: 1) The conformation of the voltage gated channels as a biphasic system, 2) the externally applied dB/dt as a subthreshold perturbation, and 3) ferritin as a source of high frequency dB/dt noise with a magnitude relevant to the typical threshold of actuation (**Figure 1d**). The most appealing feature of stochastic resonance in this case is that it does *not* require ferritin to interact with the applied magnetic field at a scale comparable to $k_B T$. Rather, the voltage induced by the applied magnetic stimulus itself could supply energy for reconfiguring the channel, and the noise generated by ferritin could merely aid in surmounting the kinetic barrier setting the threshold of actuation.

Modelling Magnetic Fluctuation and Precession in Ferritin and Comparing to Magnetite

An intriguing feature of this hypothetical mechanism is its implication that ferritin may have features that make it better suited to magnetogenetic stimulation than magnetic nanoparticles with large magnetic moments. As illustrative examples, we have selected ferritin and a 15 nm magnetite particle with a 2.5 nm polymer or silica shell. Using the stochastic Landau-Lifshitz-Gilbert (sLLG) equation to describe both precession and the influence of thermal agitation (**Figure 2a**), we model the dynamical behavior of a single particle and infer tangential B at various locations near the particle (**Figure 2b**) (Brown, 1963; Usov, 2010). Notably, this noisy signal has an additional high frequency contribution

from precession, and a low pass filter reveals behavior arising from kinetically limited reversal. Full details of this simple model can be found in the supplementary materials.

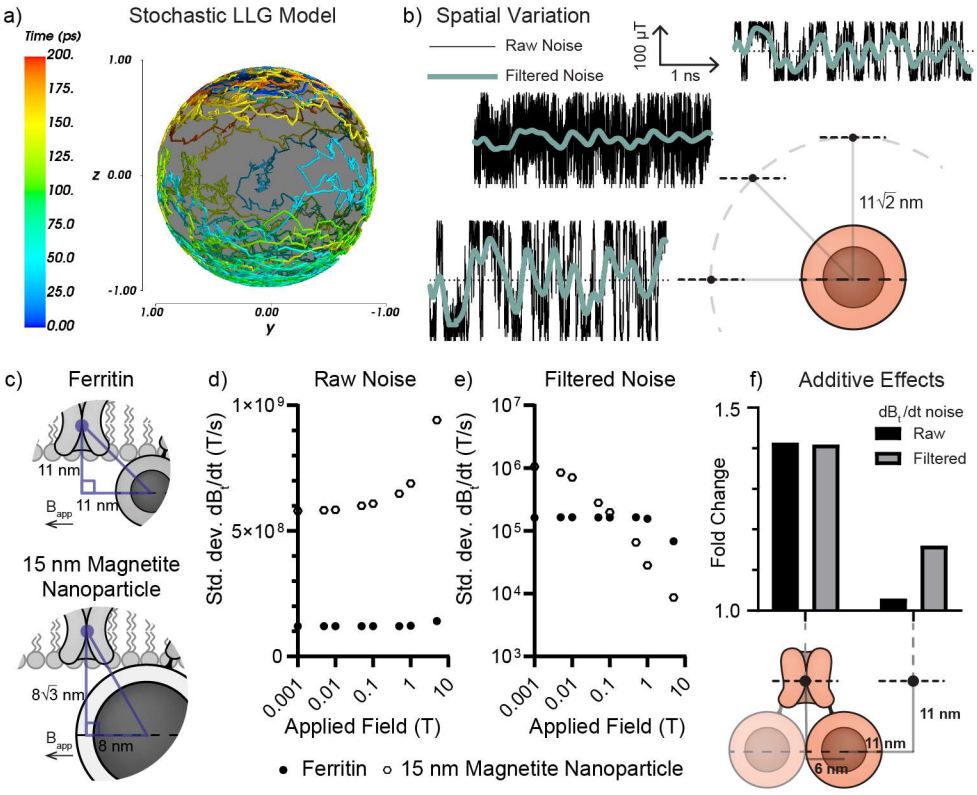

Figure 2. Simulations of noise produced by ferritin and their comparison to a 15 nm magnetite particle. **a)** 200 ps of the time evolution of the orientation of the magnetic moment of ferritin simulated with a stochastic Landau-Lifshitz-Gilbert (sLLG) model. Plot created with Mayavi in Python (Ramachandran & Varoquaux, 2011). **b)** Tangential projection of magnetic field versus time at three positions equidistant (15.6 nm) from a simulated ferritin. A low pass filter set at 10 GHz reveals signal resulting from stochastic reversal. The dashed line atop the ferritin shows the orientation of its easy axis. **c)** Simplified geometric assumptions for calculating the component of the field tangential to the membrane are shown explicitly for both a ferritin and the 15 nm magnetite particle. **d)** Standard deviation of tangential dB/dt noise for simulations of 6×10^6 steps each are shown for a range of applied quasimagnetostatic fields. The raw noise is dominated by the influence of precession. **e)** A low pass filter set at 10 GHz for ferritin and 1 GHz for magnetite was applied to the same noise data represented in panel d), and tangential dB/dt noise was calculated to show the applied field dependence of noise originating from stochastic reversal. **f)** The additive effects of noise from two adjacent non-interacting ferritins (bottom) is considered. The fold increase in the standard deviation of the noise signal is shown for two points. The first is at the center of the membrane and equidistant from the two ferritins and the other assumes similar geometry to panel c.)

Simplified geometric assumptions used for predicting tangential dB/dt noise are depicted in **Figure 2c** for both ferritin and magnetite. Since the concept of inductively coupled stochastic resonance relies upon noise sources that persist despite the external application of quasistatic fields, we considered the influence of an applied magnetic field on fluctuation. The contribution to tangential dB/dt noise arising from precession remains approximately constant or increases at sufficiently high magnitudes, as shown in **Figure 2d**. In contrast, the component arising from kinetically limited reversal is ultimately suppressed by high magnitude fields, as shown in **Figure 2e**.

Despite possessing a moment nearly 300 times weaker than the 15 nm magnetite particle, this model predicts that ferritin can nevertheless act as a comparable source of tangential dB/dt noise. If channel dynamics or other considerations make the timescale of kinetically limited reversals most relevant to actuation, ferritin may even act as a *better* source of noise than a 15 nm magnetite particle at applied fields above 100 mT (**Figure 2e**). Moreover, particles suitable for applying torques to mechanosensitive channels would typically have larger moments or require higher anisotropy, further reducing their capacity for rapid fluctuation.

In **Figure 2f**, we consider additive effects in adjacent sources of tangential dB/dt noise. At a point equidistant from each source, both filtered and unfiltered noise increase by a factor approaching $\sqrt{2}$, an expected result for the addition of two sources of uncorrelated noise with the same amplitude. The effect drops off with distance such that nearest neighbor contributions are most relevant.

Experiments to Test this Hypothesis

Although we have endeavored to frame this hypothesis as realistically as possible, we emphasize the need for further inquiry and direct experimental evidence. In this spirit, we suggest several ideas for experiments that could test various aspects.

1. The idea that ferritin is acting on voltage-gated ion channels rather than TRPV is directly testable by expressing some geometrically similar impermeable transmembrane protein incorporating ferritin in similar manner. If magnetogenetic stimulation were still observed, it would strongly suggest the relevance of interactions between ferritin and endogenous proteins. The extent of expression is clearly an important variable to consider in such an experiment. Magnetogenetically transfected neurons could serve as a positive control and wildtype neurons could serve as a negative control.

2. Applying a uniform pulsed field to in vitro samples using capacitive discharge into a suitable field coil would allow external dB/dt stimuli to be applied measurably and controllably. Observing GCaMP fluorescence to monitor neuronal response, the endogenous threshold of wild type inductive actuation could be determined. By comparing to neurons expressing abundant magnetogenetic proteins, this experiment could measure the extent to which the dB/dt threshold is lowered upon transfection.

3. To probe the mechanistic role of ferritin, it might be feasible to influence its dynamics with fields applied simultaneously with a dB/dt stimulus. If the frequency components of the

noise arising from stochastic reversal are ultimately most important, then a superimposed magnetostatic field of sufficient magnitude (greater than 2 T, **Figure 2e**) might be used to suppress inductive noise. If noise arising from precession is more important, the system could instead be driven with a microwave frequency electromagnetic field corresponding to the ferromagnetic resonance frequency of the ferritin. If either of these approaches resulted in quantifiable changes in the dB/dt threshold required for magnetogentic actuation, it would not be well explained by other proposed mechanisms (Barbic, 2019).

Conclusion

Inductively coupled stochastic resonance as a mechanism for stimulation is appealingly consistent not only with the features of some reported magnetogenetic experiments, but also with the theoretical critiques they have provoked. A few potentially important conceptual issues are left unexamined here, such as identifying which voltage gated ion channels are best suited to this form of stimulation or predicting spatial distributions of induced voltages. This hypothesis is limited to schemes employing ferritin fusions and time-varying magnetic stimuli, and offers limited or no insight into natural magnetoreception or reported magnetogenetic stimulation with constant fields.[*]

If experimental evidence were to ultimately support and refine this concept, the implications could be considerable. Most obviously, it would provide a path for rational design and optimization of magnetogenetic techniques. Additionally, time-varying fields supplied through capacitive discharge at amplitudes far below those used in transcranial magnetic stimulation could offer a low power, straightforward, and scalable approach to field generation. Such magnetic field stimuli might even be supplied by wearable devices, a consideration that would become relevant if magnetogenetics were to ultimately serve as a therapeutic technology.

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Competing interests

None to declare.

[*] Although natural occurrences such as lightning strikes can generate strong transient magnetic fields, the evolutionary context of natural magnetoreception seems to be centered on navigation in the weak geomagnetic field.

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