Modulation of Calcium Signaling and Metabolic Pathways in Endothelial Cells with Magnetic Fields

Oksana Gorobets [1,*], Svitlana Gorobets [1], Tatyana Polyakova [2] and Vitalii Zablotskii [2,3,*]

[1]National Technical University of Ukraine, "Igor Sikorsky Kyiv Polytechnic Institute", Ukraine

[2]Institute of Physics of the Czech Academy of Sciences, Prague, Czech Republic

[3]International Magnetobiology Frontier Research Center (iMFRC), Science Island, Hefei, China

*Corresponding authors: zablot@fzu.cz, gorobets.oksana@gmail.com

Abstract

Calcium signaling plays a crucial role in various physiological processes, including muscle contraction, cell division, and neurotransmitter release. Dysregulation of calcium levels and signaling has been linked to a range of pathological conditions such as neurodegenerative disorders, cardiovascular disease, and cancer. Here, we suggest that in the endothelium, calcium ion channel activity and calcium signaling can be modulated by applying either a time-varying or static gradient magnetic field (MF). This modulation is achieved by exerting magnetic forces or torques on either biogenic or non-biogenic magnetic nanoparticles that are bound to endothelial cell membranes. Since calcium signaling in endothelial cells induces neuromodulation and influences blood flow control, treatment with a magnetic field shows promise for regulating neurovascular coupling and treating vascular dysfunctions associated with aging and neurodegenerative disorders. Furthermore, magnetic treatment can enable control over the decoding of Ca signals, ultimately impacting protein synthesis. The ability to modulate calcium wave frequencies using MFs

and the MF-controlled decoding of Ca signaling present promising avenues for treating diseases characterized by calcium dysregulation.

Keywords calcium signaling, biogenic magnetic nanoparticles, wall shear stress, magnetic field, magnetic switching, frequency bands decoding proteins

Introduction

The ability to process information at the cellular and subcellular levels is fundamental to important processes in living organisms - from cell fertilization and division to short-term memory, aging, and the development of many diseases. Biological information transfer and control of processes in living organisms occur through physiological oscillations, which can take the form of individual spikes, periodic oscillations, and propagating waves. The mechanisms underlying such physiological oscillations and their roles remain largely unknown [1]. A vast amount of experimental evidence has accumulated regarding calcium oscillations, which demonstrate the crucial role of calcium ion signals in all levels of structural organization of the organism, from subcellular to large-scale calcium spikes and waves in neurons of the brain [2] and long-range calcium signals in plants [3,4]. Calcium signals, which propagate as concentration waves of calcium, direct the functioning of the entire organism, starting from the moment of the emergence of life when sperm introduce phospholipase C-ζ into the egg and a slow oscillating wave of Ca^{2+} moves through the egg cell, triggering fertilization [5,6], and ending with its extinction, accompanied by calcium necrotic waves that contribute to the death of the organism [7]. During the development and life of an organism, biological information is transmitted through frequency-modulated waves of calcium, similar to radio signals [5]. This information is encoded through a complex set of channels and transporters using specific frequency modulation of calcium waves, and then

transmitted to receivers, where it is decoded by several sensors and effectors, resulting in a conversion into specific cellular processes and metabolic pathways.

Despite extensive knowledge accumulated about the mechanisms of information processing transmitted by calcium signals, the principles of its encoding and decoding remain largely unclear. It seems that in most cases, the transmission of biological information follows a principle exemplified by the activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), an enzymatic complex consisting of dimers of hexameric rings. CaMKII is particularly sensitive to the frequency of intracellular Ca^{2+} oscillations, where only high-frequency oscillations provide sequential and autonomous activation of individual catalytic domains, and the duration or amplitude of the pulse does not affect its activation [8]. The process of decoding is based on the kinetics of calcium binding and unbinding to kinases and phosphatases, which, respectively, activate and deactivate target proteins [5]. Each molecule involved in decoding Ca^{2+} oscillations can recognize oscillatory patterns within a specific frequency range. Different decoding proteins have their own specific frequency ranges (with only a small overlap between them), indicating their specific roles in cells, such as activating specific cellular programs. Therefore, different frequency ranges correspond to different Ca^{2+} binding proteins that control different metabolic processes and generate different cellular signals. The frequencies of intracellular Ca^{2+} oscillations are specific to each cell type and range from about 1 mHz in endothelial cells to about 1000 mHz in cardiac cells and neurons [5,9]. The frequency of calcium oscillations determines the pace of the body's biological clocks. In neuronal networks, the frequency of Ca-mediated spike oscillations plays a crucial role in determining biological timing and organisms' perception of time. Spike oscillations in neuronal circuits are tightly regulated and synchronized, facilitating various cognitive processes such as attention, memory, and decision-making [10,11].

As oscillating calcium signals are associated with an individual's cognitive abilities and memory, and magnetic fields (MFs) are capable of affecting the dynamic patterns of calcium, such as releasing calcium from intracellular depots and increasing its concentration in the cytosol [12–15], the influence of magnetic fields

on cognitive processes such as improving attention, memory, and decision-making abilities [16–18] no longer seem as unexpected as they might at first glance. The transmission of calcium signals is a crucial component of brain plasticity and is involved in various forms of plasticity, including synaptic plasticity, neurogenesis, and dendritic branching [19]. In the heart, calcium oscillations play a critical role in regulating heart rate and rhythm [20]. The treatment of human umbilical vein endothelial cells with a rotating magnetic field (4 Hz and 0.2 T) demonstrated an increase in intracellular Ca^{2+} concentration. When *Caenorhabditis elegans* was exposed to this magnetic field for a prolonged period (hours), it surprisingly resulted in an extended lifespan [21]. Overall, calcium oscillations represent a universal and fundamental signaling mechanism that plays a decisive role in various physiological processes in living beings.

Disruptions in Ca signaling can lead to the development of various diseases such as osteoporosis, arterial hypertension, cardiac arrhythmia, diabetes, and neurological disorders including Alzheimer's and Parkinson's diseases. By properly modulating the frequency of Ca signal transmission, specific pathways and processes involved in the development or progression of many diseases can be pharmacologically targeted. For example, drugs that increase or decrease the frequency of Ca oscillations can be used to target specific types of cancer cells [22]. In addition, modulating Ca signal transmission can help reduce inflammation in autoimmune diseases by regulating the function of immune cells [23]. However, to date, there is no universal mechanism or physical tool that allows for selective control of calcium ion channels, thereby modulating calcium oscillations and waves to achieve therapeutic effects. The main problem here is how to achieve a suitable frequency setting for calcium oscillations to achieve a controlled change in metabolic pathways and affect not only cell function but also its fate, for example, by inducing apoptosis or slowing down the process of cell division.

In this work, we suggest a disruptive idea: a non-invasive method for modulating calcium signal oscillations using magnetic fields. Through theoretical modeling and computer simulations, we found magnetic field regimes that provide frequency or amplitude modulation of ion channel activity and waves of free calcium

concentration. We show how with suitable tuning of calcium oscillation frequencies, it is possible to selectively control the decoding protein functions and the synthesis of related proteins. These results expand our understanding of the mechanisms of ion channel activation and inactivation and can serve as a reliable theoretical basis for developing new approaches to treating a wide range of human diseases.

Results

Model and mechanisms of MF impacts on ion channels

We now construct a mathematical model of the MF influence on the key intracellular and extracellular processes incorporated in Ca^{2+} dynamics. We start with the robust models of Plank et al. (2006) [24] and Wiesner et al. (1996) [25], which have been verified by numerous experiments on Ca^{2+} dynamics [26–30].The basic equations of our model are given in the Section 4 (Method). Our generalization of the model [24] takes into account the following key factors that are influences by a MF. The first, the existence of biogenic magnetic nanoparticles (BMNs) practically in all organs of organisms [31–37], Fig. 1. The second, in an organism, the BMNs self-assemble into chains mainly located on lipid membranes of endothelial [38], cardiac [39] and other cells [40]. The third, many types of membrane ion channels are sensitive to small shear stress which can gate these channels [41]. Finally, when an external magnetic field is applied, it causes mechanical forces to act on BMN chains. These mechanical forces are then transmitted into the cell membrane, causing shear stress within it. Sources of BMNs are: aging (as the body ages, mitochondrial dysfunction in cells increases iron accumulation in various tissues and causes iron-dependent brain degeneration [42]), hypoxia, environmental contamination [43,44], magnetic nanoparticles injected as contrast agent at MRI [45,46], etc. It should be noted that mechanical shear stress in a cell membrane directly affects calcium influx, q_{in} as described in model [24] by Eq. 11 in the Method Section.

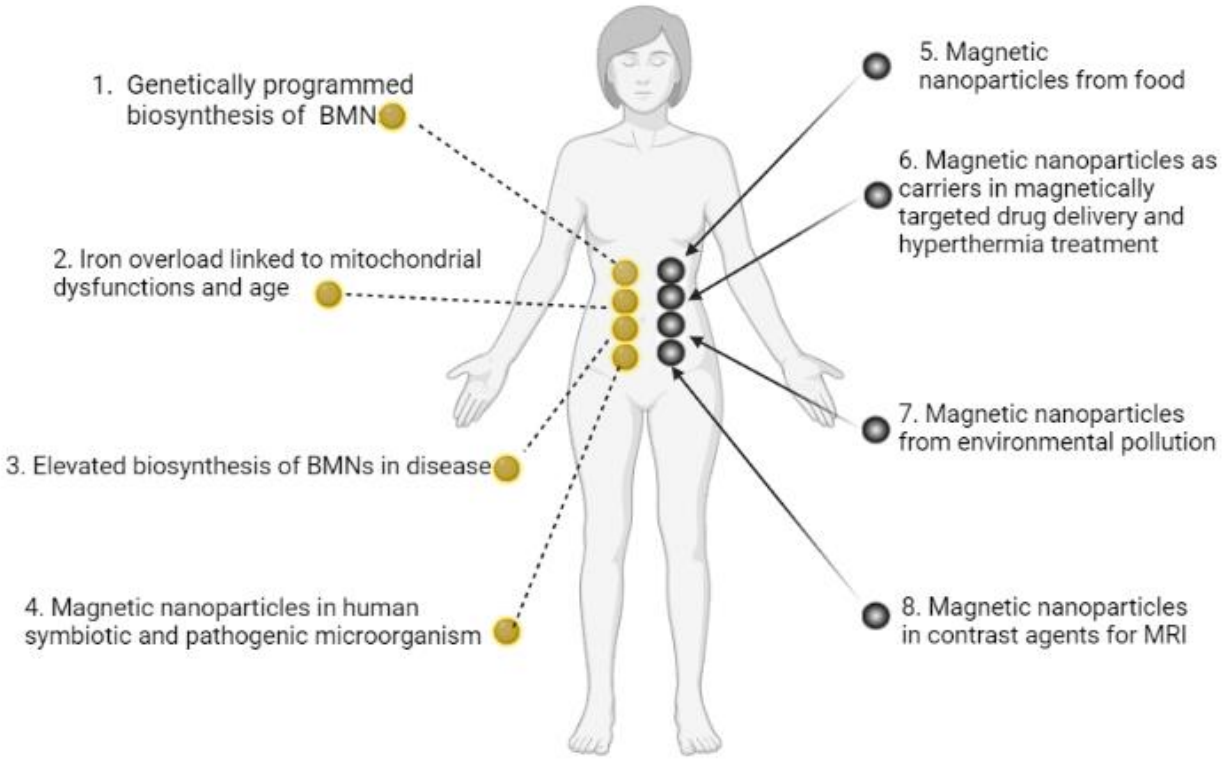


Fig. 1. Origins of BMNs and other magnetic nanoparticles in an organism. 1. Genetically programmed biosynthesis of chains of biogenic magnetic nanoparticles [33,47–51], see also the review paper [37]. 2. Iron overload linked to mitochondrial dysfunctions and age-related diseases [42] 3. Elevated biosynthesis of biogenic magnetic nanoparticles in disease (a number of neurodegenerative diseases and cancer) [32,52–54], see also the review paper [37]. 4. Magnetic nanoparticles in human symbiotic and pathogenic microorganism [55,56]. 5. Magnetic nanoparticles from food (plant [57]), mushroom [58], animal [59]). 6. Magnetic nanoparticles as carriers in magnetically targeted drug and cell delivery (see the review papers [60–64]) and hyperthermia [65,66]. 7. Magnetic nanoparticles from environment pollution [43,44]. For example, airborne magnetite pollution particles < ~200 nm in size can access the brain directly via the olfactory and/or trigeminal nerves, bypassing the blood-brain barrier [44]. 8. Magnetic nanoparticles in contrast agents for MRI [45] [46]. In particular, BMNs are experimentally revealed in human brain [31,32], heart [33], liver [33], spleen [33], ethmoid bone [34], adrenal glands [35]. BMNs in animals and human are chemically pure magnetite or maghemite and was found to be organized into magnetically interacting clusters and

linear membrane-bound chains [38,67–69] as well as BMNs in magnetotactic bacteria. For example, human brain contains the intracellular magnetite crystals forming chains and are bound to the cell membrane, and have a saturation magnetization Ms = 4.5×10^5 A/m [70]; there are up to 80 magnetite crystals in a chain in the human brain according to [71]. The chains of BMN are found experimentally in capillary walls that are formed by a single layer of endothelial cells [38]. In pathology, biogenic magnetic nanoparticles are revealed in tumour tissue in high amounts [32,72] at the cell membrane [73].

The key processes incorporated in the model of Ca^{2+} dynamics (see Fig. 2 for a schematic representation) are the following [24]. 1. The internal production of IP3, which includes several processes such as the activation of a G-protein and phospholipase C and the cleavage of PIP_2. 2. IP3 opens Ca^{2+} channels in the endoplasmic reticulum (ER). 3. Both the rate of IP3 production and the rate of internal Ca^{2+} release can be enhanced by cytosolic free Ca^{2+}. 4. The influx rate of Ca^{2+} due to the process termed capacitive calcium entry [74] is an increasing function of the degree of depletion of the ER below resting levels, as well as the Ca^{2+} concentration difference across the plasma membrane. 5. The rate of Ca^{2+} influx through shear-gated channels is an increasing function of the mechanical shear stress to which endothelial cells are exposed. 6. Cytosolic Ca^{2+} is resequestered back into the ER by a Ca^{2+}- ATPase and is pumped out of the cell by a plasma membrane Ca^{2+}- ATPase and Ca^{2+}- Na^{+} exchanger. 7. Cytosolic Ca^{2+} is reversibly buffered to proteins such as calmodulin. In Section 4 (Method), these processes are mathematically described by the system of differential equations (10-13). The wall shear stress (WSS) is also engaged in these equation and WSS plays a significant role in the regulation of calcium dynamics [24,25]. To take into account effects of MFs, in Eqs. (10-13), we add the magnetic-field-induced shear stress to that induced by blood flow as

$$\tau = \tau_h + \tau_{magn}, \tag{1}$$

where τ_h is WSS induced by hydrodynamic blood flow in an endothelial cell (the typical values of WSS of blood flow in a vessel are $\tau_h = 1$ Pa for artery and $\tau_h = 0.1$ Pa [75] for capillary), τ_{magn} is WSS induced by the magnetic forces acting on the chain of magnetic nanoparticles embedded in cell membrane. Further, we consider the WSS induced by gradient and uniform MFs.

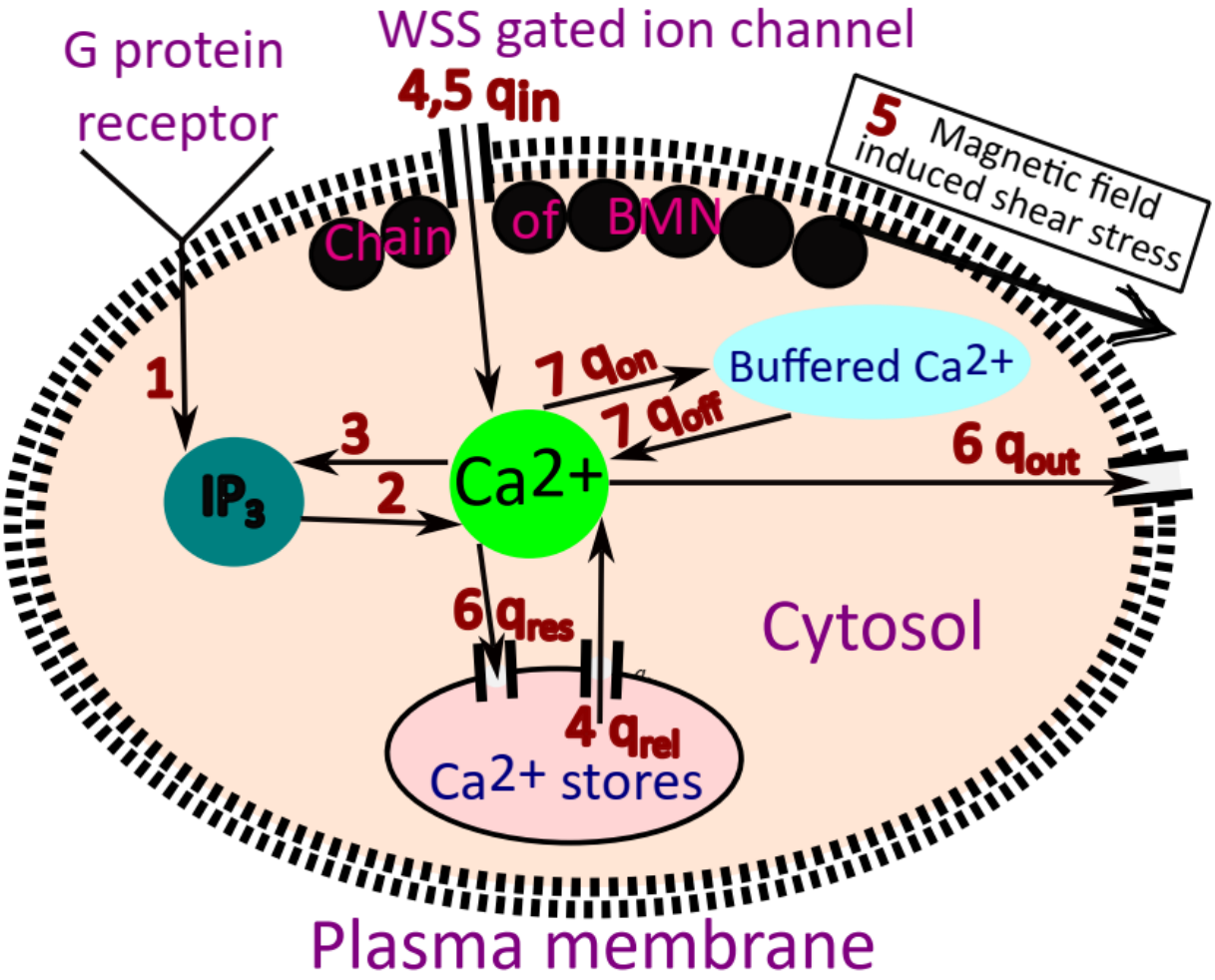


Fig. 2. Schematic image of a magnetic nanoparticle chain at the cell membrane and influence of magnetic MF-induced shear stress on mechanosensitive ion channel gating and on the rates of Ca^{2+} fluxes in an endothelial cell. The key processes incorporated in the model of Ca^{2+} dynamics are numbered from 1 to 7 (for details, see the text and Table 1, Table 2).

High magnetic WSS hypothetically may result in detachment of magnetic nanoparticles from the membrane. The estimation of the magnetic field flux density and gradient for detachment of magnetic nanoparticles is an open question. Inverse MF field effect on ion channel gating disappears if inverse magnetic field is equal to coercive force and the chain magnetization is zero, $B_c \approx 5 - 140$ mT, $\frac{\pi}{2} < \gamma \leq \pi$, $B = \frac{B_c}{sin\theta|cos\,\gamma|}$.

Below we show theoretically how to modulate ion channels activity and modulate calcium signaling frequency with uniform and gradient magnetic fields.

Ca^{2+} ion channel gating by MFs through wall shear stress

In Eqs. 1-3, to describe analytically Ca^{2+} influx we utilize the model [24], which explores the response of membrane ion channels to shear stress. The application of shear stress induces a uniaxial tension gradient in the membrane and deforms it. The deformation of the membrane imparts a strain energy density, *W*, which depends upon the applied shear stress. The fraction of channels in the open state depends on the strain energy density as follows [25]:

$$f_o(\tau) = \frac{1}{1+\alpha\, exp\left(-\frac{f_e W(\tau)}{kT_e N}\right)} \tag{2}$$

where τ is applied wall shear stress (WSS), *N* is channel density per unit area of cell membrane, *k* is the Boltzmann constant, T_e is the absolute temperature, and α ($\alpha \geq 0$) is a measure of the probability that a channel is in the open state in the no-load case, namely, $(1+\alpha)^{-1}$ is the probability that a channel is in the open state in the no-load case *W*=0, f_e $(0 \leq f_e \leq 1)$ is the fraction of the energy of the membrane that gates the WSS-sensitive Ca^{2+} channels.

The strain energy density function has the form for a two-dimensional membrane [25,76] (Fig. S1, Fig. S2):

$$W(\tau) = \frac{\left[\varepsilon'\tau l + \sqrt{16\delta^2 + \varepsilon'^2\tau^2 l^2} - 4\delta\right]^2}{8\left[\varepsilon'\tau l + \sqrt{16\delta^2 + \varepsilon'^2\tau^2 l^2}\right]} \tag{3}$$

where ε' is the fraction of the applied load borne by submembranous structures, δ is membrane shear modulus, l is cell length in the flow direction.

The shear-dependent Ca-influx is proportional to the fraction of open Ca^{2+} channels in the plasma membrane [25], which has a Boltzmann dependence [77] on the strain energy density in the plasma membrane $W(\tau)$. This gives a sigmoidal relation between WSS-dependent Ca-influx and the applied WSS. Consequently, the following expression is valid for Ca^{2+} influx [24]:

$$q_{in} = k_{CCE}\left(Ca_{s,0} - Ca_s\right)\left(Ca_{ex} - Ca_c\right) + \frac{q_{\max}}{1+\alpha \exp\left(-\frac{f_e W(\tau)}{kT_e N}\right)} \tag{4}$$

where Ca_s is concentration of Ca^{2+} in the internal stores, $Ca_{s,0}$ is an initial value of the concentration of Ca^{2+} in the internal stores, Ca_c is concentration of free Ca^{2+} in the cytosol, Ca_{ex} is concentration of external Ca^{2+}, k_{CCE} and $q_{\max}$ are the constants.

Let us calculate the WSS in (2) and (3) induced by gradient magnetic field application. First, we consider a chain of magnetic nanoparticles embedded in cell membrane under influence of a gradient magnetic field (Fig. 2, Fig. 3A).

The magnetic gradient force is $\vec{F} = N\left(\vec{p}_m\vec{\nabla}\right)\vec{B}$, $\vec{p}_m$ is the magnetic nanoparticle magnetic dipole moment, *N* is the number of magnetic nanoparticles in the chain, $\vec{B}$ is the magnetic field induction. The WSS is $\tau_{magn} = \frac{F_\tau}{N\pi r^2}$ where F_τ is the in-plane component of magnetic gradient force, *r* is the magnetic nanoparticle radius. Then, in a gradient MF the stress is

$$\tau_{magn} = \frac{4rMG\sin\theta_0}{3} \cdot cos(\omega t), \tag{5}$$

where M is magnetization of magnetic nanoparticle (which is a function of applied magnetic field), $G = \left|\frac{\partial\vec{B}}{\partial z}\right|$, θ_0 is the angle between $\frac{\partial\vec{B}}{\partial z}$ and the normal to the plane of membrane in the case when z-axis is chosen along

the direction of $\vec{M}$ (Fig. 3 A). The parameter G characterizes MF gradient and it is considered as oscillating harmonic function, the case of constant MF gradient is described by formular (5) at $\omega = 0$.

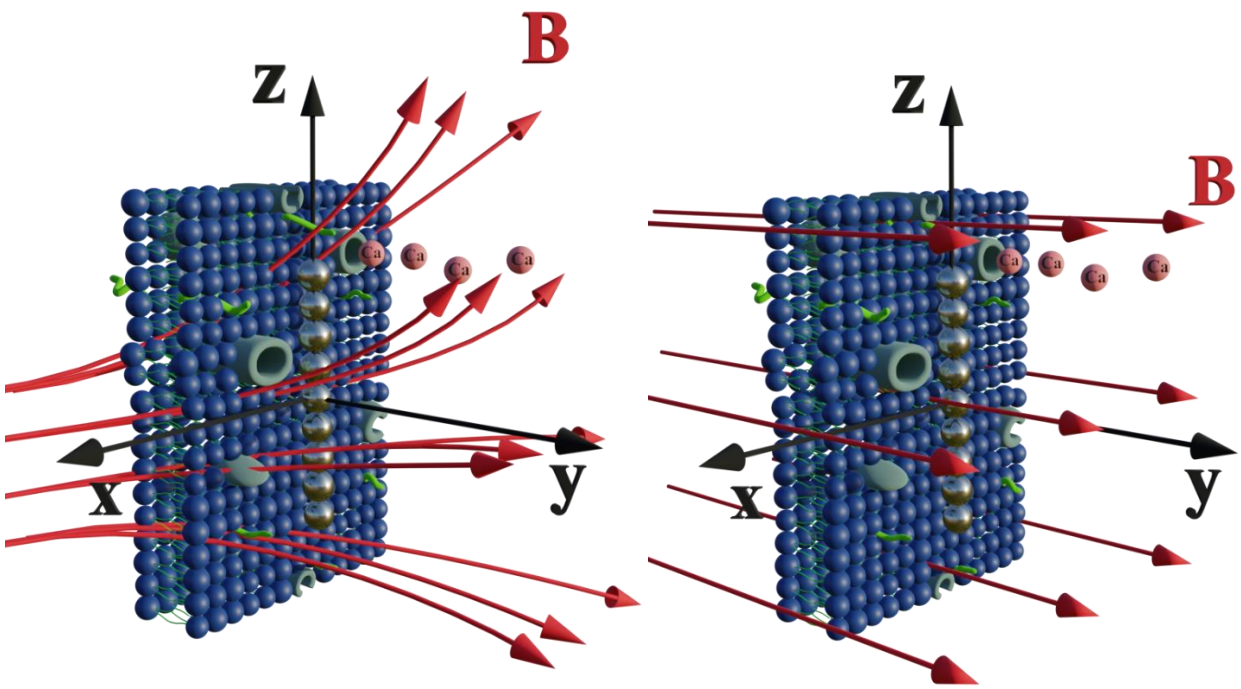
Now we calculate the WSS in (3) induced by uniform magnetic field application. We consider a chain of magnetic nanoparticles embedded in a cell membrane under the influence of a uniform MF (Fig. 3 B).

The torque of magnetic force can be written as a vector sum of its in-plane and out-of-plane components $\vec{M}_F = \vec{M}_{F,\tau} + \vec{M}_{F,n} = [\vec{M} \times (\vec{B}_n + \vec{B}_\tau)]V$, where $V = \frac{4}{3}\pi r^3 N$, $\vec{M}_{F,n} = [\vec{M} \times \vec{B}_n]V$, $\vec{M}_{F,\tau} = [\vec{M} \times \vec{B}_\tau]V$, $\vec{B}_n = (\vec{B} \cdot \vec{n})\vec{n}$ is out-of-plane component of magnetic field flux density, $\vec{B}_\tau$ is the in-plane component of magnetic field flux density, $|\vec{B}_\tau| = |[\vec{B} \times \vec{n}]| = Bsin\theta$; $M_{F,\tau} = MBV\, sin\,\theta\, sin\,\gamma$ is the absolute value of in-plane component of the torque of magnetic force producing WSS (Fig. 3 B). Then in the case of uniform magnetic field

$$\tau_{magn} = \frac{\pi}{6N} MB \sin\theta sin\gamma \cdot cos(\omega t), \tag{6}$$

where θ is the angle between the normal to the cell membrane and MF direction, γ is the angle between the MF in-plane component and magnetization of the chain of magnetic nanoparticles (Fig. 3 B). In Eq.9, in a general case, the magnetic field flux density is considered as oscillating harmonic function, while for a static MF $\omega = 0$.

It should be noted here that even for a low magnetic field (MF) such as the geomagnetic field, the shear stress is not small. For example, an estimate (Eq. 9) gives a magnitude of shear stress of about 1.3 Pa for the geomagnetic field *B*=0.05 mT and $N = 10$, $r = 100\ nm$, $M_S = 510$ kA/m.



A B

Fig. 3. Schematic of a chain of magnetic nanoparticles on a cell membrane under the influence of a) gradient and b) uniform magnetic field. Two calcium ion channels are depicted in the vicinity of the chain. The red arrows are magnetic lines.

Thus, Eqs. 8 and 9 describe magnetically induced shear stress in the cell membrane for gradient and uniform MFs, accordingly. Both stresses depend on the MF direction and magnitude. For the certain directions of an uniform MFs the shear stress is zero: ($\theta = 0, \theta = \pi$), ($\gamma = 0$ or $\gamma = \pi$). There are also two critical MF magnitudes at which shear stress is zero. The first, an MF with the z-component antiparallel to the initial magnetization of BMN chain which is equal to the BMN coercive field. The second, a uniform MF with a magnitude which exceeds the saturation magnetic field of BMNs. See Supplemental Material at [URL will be inserted by publisher] for explicit expressions and numerical values of these critical fields.

In a gradient MF, shear stress (Eq. 8) can close/open the membrane ion channels. In such a case, for high MF gradients, the effect of "magnetic saturation of channels" is expected: a high enough magnetic shear stress (Eq. 8) keeps ion channels in the fully opened state [78].

Let us introduce the upper limit of the WSS which keeps the channels in the open state. Strictly speaking, as dictates Eq. 7, a channel is fully open when the energy associated with shear stress, *W* goes to infinity. In this case, we can define the open state probability, for example as f_0=0.9. Thus, by this definition, 90 % of channels are open at the certain value of shear stress, which we call as stress of the channel saturation, P_s. See Supplemental Material (Fig. S4) at [URL will be inserted by publisher] for estimation of the Ca++ channel saturation reached at $P_s \approx 5$ Pa in endothelial cells.

Below we introduce two dimensionless parameters controlling the magnetic field influence on membrane chains of magnetic nanoparticles and the gating of mechanosensitive Ca^{2+} ion channels and intracellular Ca dynamics.

The first parameter is $m = \frac{P_{mag}}{P_s}$ where the expression P_{mag} is the amplitude of magnetic WSS (for definition see Section 4, Methods), and P_s is the WSS corresponding to saturation of the current through the mechanosensitive Ca^{2+} ion channel assuming the probability of channel opening $f_o = 0.9$ in Plank's model (Fig. 2). The parameter m is used for both cases: WSS induced by a gradient magnetic field and for WSS induced by uniform magnetic field. For both cases, the magnitudes of magnetic WSS are given by the expressions (5 a) and (6 c) in Section 4, Methods.

The second parameter is $\mu = \frac{P_s}{\tau_h}$, where τ_h is WSS due to blood flow in a vessel, e.g., $\tau_h = 1$ Pa for artery and $\tau_h = 0.1$ Pa [75] for capillary. The second parameters μ is independent of a MF and therefore serves as a material parameter. We estimate this ratio to be $\mu \approx 5$ for artery and $\mu \approx 50$ for capillary. Thus, the calcium dynamics differs significantly for artery and for capillary both for oscillatory regime and non-oscillatory regime parameters given in Table S2.

The next important parameter describing the MF influence on calcium dynamics is the frequency of oscillation of magnetic field, ν. Thus, our further results on Ca^{2+} dynamics we map in the coordinates (*m*,ν) for different values of the μ-parameter related to different endothelial cells.

The further results and discussion we report for endothelial cells taking on account the set of parameters of Plank's model [24] describing the gating of Ca^{2+} ion channels and intracellular Ca dynamics in endothelial cells (Table S2).

Endothelial Ca^{2+} dynamics

Vascular endothelial cells, which form the inner lining of the blood vessel wall and are directly exposed to blood flow and corresponding shear stress, serve crucial homeostatic functions in response to various chemical and mechanical stimuli [78,79]. Hence, our subsequent analysis is centered on investigating the dynamics of Ca^{2+} in endothelial cells. Without a MF, dynamics of the concentration of free calcium in the cytosol is characterized by a stable fixed point in non-oscillatory regime and by a stable periodic orbit in oscillatory regime [24]. A non-constant solution of dynamic equations is periodic if there exists a constant T>0 such that all dynamic variables have the same values at time t *and* $t+T$ for all t . The period of this solution is defined to be the minimum such T . The image of the periodicity interval [0,T] for dynamic variables in the state space R^n is called the periodic orbit or cycle. Thus, a certain transition time is needed for the free calcium concentration to achieve the fixed-point value or the stable periodic orbit.

To reveal the effects of low-frequency MF on the concentration of free Ca^{2+} in cytosol we solve numerically Eqs. 10-13 with regard to Eqs. 7-9. The results of calculations are mapped onto the (*m,v*)-diagrams (Fig. 4). Here, for different MF amplitudes (related parameter is *m*) and frequencies ν we demonstrate: the maximum amplitude of spike of free cytosolic calcium concentration $Ca_c^{(\max)}$, the time averaged amplitude of spike of free cytosolic calcium concentration $\left\langle Ca_c^{(ampl)} \right\rangle$, the time averaged concentration of free cytosolic calcium $\left\langle Ca_c \right\rangle$, and the time averaged frequency of quasiperiodic spikes of free cytosolic calcium concentration

$\left\langle \nu_{Ca_c} \right\rangle$. The chosen ranges of MF frequencies, from 6 mHz to 17 mHz, correspond to the optimal specific frequencies of decoding enzymes: 1) MAPK, 2) NF-κB, 3) NFAT, 4) glycogen phosphorylase kinase [5]. It is important to note that the frequency range (≈10 mHz) of the decoding enzymes is determined by molecular motor dynamics in which the typical binding rates are (1-5) 10^{-2} s^{-1} [80]. The upper limit of the signaling frequency is related to the time scale (Δt=1/ν) corresponding to the mean time of calcium waves propagations in cell, which is estimated as L/u ≈ 20 μm/20 μm s^{-1}= 1 s for the velocity of calcium waves, u= 20 μm s^{-1} [81].

Sensing frequencies of decoding proteins

In human aortic endothelial cells, the frequency of agonist-induced Ca^{2+} oscillations is positively correlated with the NF-κB activity in the range of 1.8–5.3 mHz, with a duration of approximately 160 s (duty cycle 0.29–0.85) [5]. Using another experimental setup with Ca^{2+} clamping in combination with agonist stimulation, vascular endothelial cells were shown to regulate VCAM1 expression with a Ca^{2+} frequency in the range of 1.7–11.7 mHz, with a duration of approximately 29 s (duty cycle 0.049–0.34) [5]. In human cerebral endothelial cells treated with sarco/endoplasmic reticulum Ca^{2+}-ATPase and inositol 1,4,5-trisphosphate receptor (InsP3R) inhibitors to modulate the Ca^{2+} frequency, the NF-κB activity is positively correlated with frequencies in the range of 0–5.2 mHz (duration 100 s) [5]. Histamine was also used in human aortic endothelial cells showing that the NF-κB activity is positively correlated with Ca^{2+} frequency in the range of 2–4 mHz (duration 60 s) [5]. There are the following decoding proteins of Ca^{2+} oscillations in endothelial cells: NFAT, NF-κB, MAPK and glycogen phosphorylase kinase [5]. The sensing frequencies of these proteins are listed below [5]. MAPK (mitogenactivated protein kinase). Ca^{2+} frequencies in the range of 1.7–17 mHz with a duration of approximately 50 s (duty cycle 0.085–0.85). NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cell) the Ca^{2+} frequency in the domain of 0.56–10 mHz, with a duration of approximately 100 s (duty cycle 0.028–0.5) [5]. Notably, the minimum frequency is 4.5 times lower than for NFAT [5]. The main difference between NFAT and NF-κB is the higher sensitivity of NF-κB, where frequencies as low as 0.56 mHz suffice [5]. NF-κB seems to be tuned toward higher duty cycles (0.8–0.9) than NFAT. The optimal frequency

is around 10 mHz [5]. NFAT (nuclear factor of activated T-cells) is activated by the phosphatase calcineurin, frequencies in the range of 2.5–10 mHz, with a duration of 50 s (duty cycle 0.125–0.5). The maximum NFAT activity is present at the Ca^{2+} frequency of 16.7 mHz (duty cycle 0.33) with decreasing activity down to 2 mHz and up to 33 mHz, with a duration of 20 s (duty cycle 0.04–0.66). The optimal frequency is approximately 20 mHz and duty cycle around 0.2–0.3. GP (Glycogen phosphorylase) is activated by a kinase that has a calmodulin-like Ca^{2+} sensitive domain, frequency interval of 1.7–170 mHz, whereas the enzyme shows constant activity at higher and lower frequencies [5].

Shift of the Ca^{2+} spiking frequency in MFs

The (m, ν) - diagrams (Fig. 4) demonstrate that the MF influence on intracellular Ca dynamics in both oscillatory and non-oscillatory regimes (Fig. S3 A, Fig. S3 B). The appearance of either the oscillatory or non-oscillatory regime is determined by the actual values of both parameters: *m* and μ, and parameters of the Plank's model not dependent on MF (Table S2). In the non-oscillatory regimes (in Fig. 4, typically domains with low *m*), the average Ca^{2+} concentration and its standard deviation from the average value doesn't depend on the MF frequency, ν.

In the oscillatory regimes, the average Ca^{2+} concentration, the amplitude and frequency of Ca oscillation depend on the MF frequency in a resonant-like manner (Fig. 4, Fig. 5 (A, B, C, D, E, F)). In Fig. 4, the diagrams show the frequency ranges for which the magnetic field effects on Ca^{2+} concentration are more pronounced. The drastic influence of magnetic field on Ca dynamics takes place at low frequencies that are comparable with the frequency of Ca concentration self-oscillations without a magnetic field. This result is in qualitative agreement with the experimental data [82] that the effects of magnetic influence on spectral power of the cytosolic Ca^{2+} oscillator was observed at low frequencies (within the 0–10 mHz subinterval of the Ca^{2+} oscillation spectrum) [82]. However, for the high frequency ranges (Fig. 4), the change Ca concentrations caused by the MFs (Fig. 6 (A, B, C, D, E, F)) are not significant, which also in a good agreement with experiment [82].

Both the so-called foldover effect and superharmonic resonance are seen in the diagrams (Fig. 4). In general, they represent a distinct feature of nonlinear oscillators that do not oscillate sinusoidally. In such systems, the oscillation is not a single sinusoidal wave, but rather a combination of sinusoidal waves with frequencies that are whole number multiples of the fundamental frequency. In our case, the first resonant frequency, $\nu \approx 0{,}009$ Hz in Fig. 4 A, C corresponds to the frequency of the first maximum in amplitude spectrum of the temporal dependence of the free Ca^{2+} concentration for an artery without MF as obtained with a discrete Fourier transform after the subtraction of the average Ca^{2+} concentration (see Supplemental Material at [URL will be inserted by publisher] for *.zip file containing the python project *MagniCa*). The second resonant frequency, $\nu \approx 0{,}013$ Hz (Fig. 4 A, C) corresponds to the frequency of the second maximum in amplitude spectrum of the temporal dependence of the free Ca^{2+}concentration for the artery without MF based on a discrete Fourier transform after the subtraction of the average Ca^{2+} concentration.

In Figs. 4, in (A, C, E) diagrams calculated for arteria, for the intermediate MF frequencies (10-12 mHz) and the *m*-parameter lying in the range 0.75-1, one can see the domain in which the amplitude of oscillation of cytosolic calcium reaches its maximum. For capillaries (Figs. 4, (B, D, F)), in the same frequency and *m* domain. The cytosolic calcium concentration is only slightly increased by the MF influence. The average frequencies of Ca^{2+} ion channel gating as a function of *m* and ν (which is MF frequency) are shown in Fig. 4 E and Fig. 4 F, for arteries and capillaries, accordingly. There is the threshold *m*(ν)- curve on reaching which the oscillation frequency of cytosolic Ca^{2+} sharply doubles. Physically, the doubling of Ca^{2+} oscillation frequency is associated with the saturation of ion currents through Ca channels on reaching *m*=1 (Fig. 4 E, Fig. 4 F), which, in turn, is a direct consequence of the effect of Ca^{2+} ion current saturation under high WSS (a high enough magnetic shear stress (Eq. 8) keeps ion channels in the fully opened state [78]. In the other words, if m approaches unity the magnetic WSS value achieves the saturation stress, $P_s = 5\ Pa$ at which the Ca2+ ion channels are open with probability 0.9. For example, the ion current saturation of takes place in MFs with the gradient $G_0 \approx 80$ T/m and BMNs with $r = 100$ nm, $M_s = 510 \cdot 10^3$ A/m. In both cases, for arteria (Fig. 4 E) and capillaries (Fig. 4 F), after the frequency doubling, the further increase of a MF or its gradient doesn't lead to

an increase of the rate of cytosolic Ca^{2+} oscillations and doesn't affect intracellular Ca dynamics (Fig. 4, E and F).

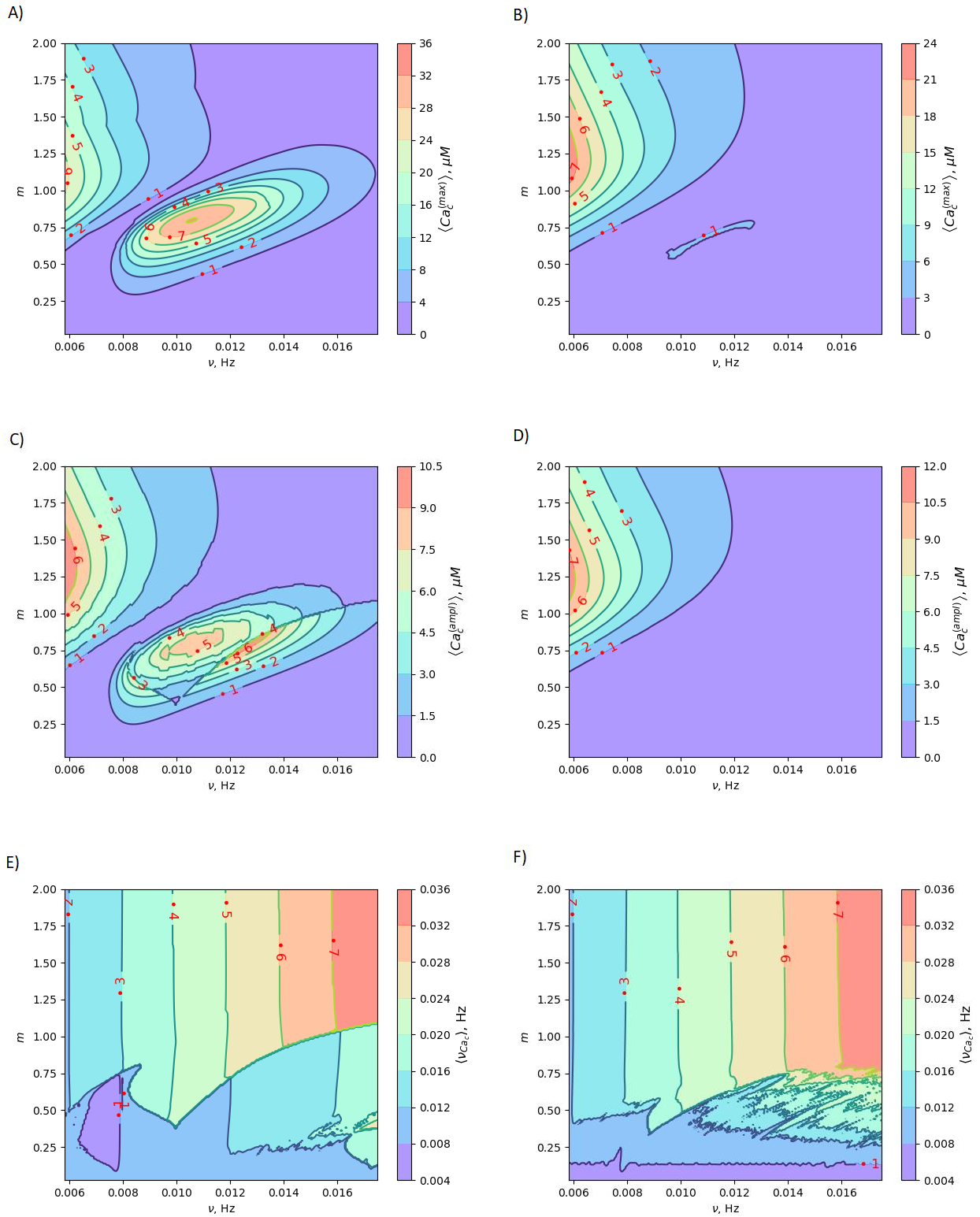


Fig. 4. Mapping MF effects on dynamics of intracellular free Ca^{2+} concentration in the vascular endothelium: for artery (left column) and for capillary (right column) in low-frequency MF. The parameters used in the calculations are listed in Table S2. Here, ν is the MF frequency, $\langle \nu_{Ca_c} \rangle$ is time averaged quasi-frequency of oscillations of free cytosolic Ca^{2+} concentration, $\left\langle Ca_c^{(ampl)} \right\rangle$ is time averaged amplitude of the spike of free cytosolic Ca^{2+} concentration, $\left\langle Ca_c^{(max)} \right\rangle$ is maximum amplitude of the spike of free cytosolic Ca^{2+} concentration.

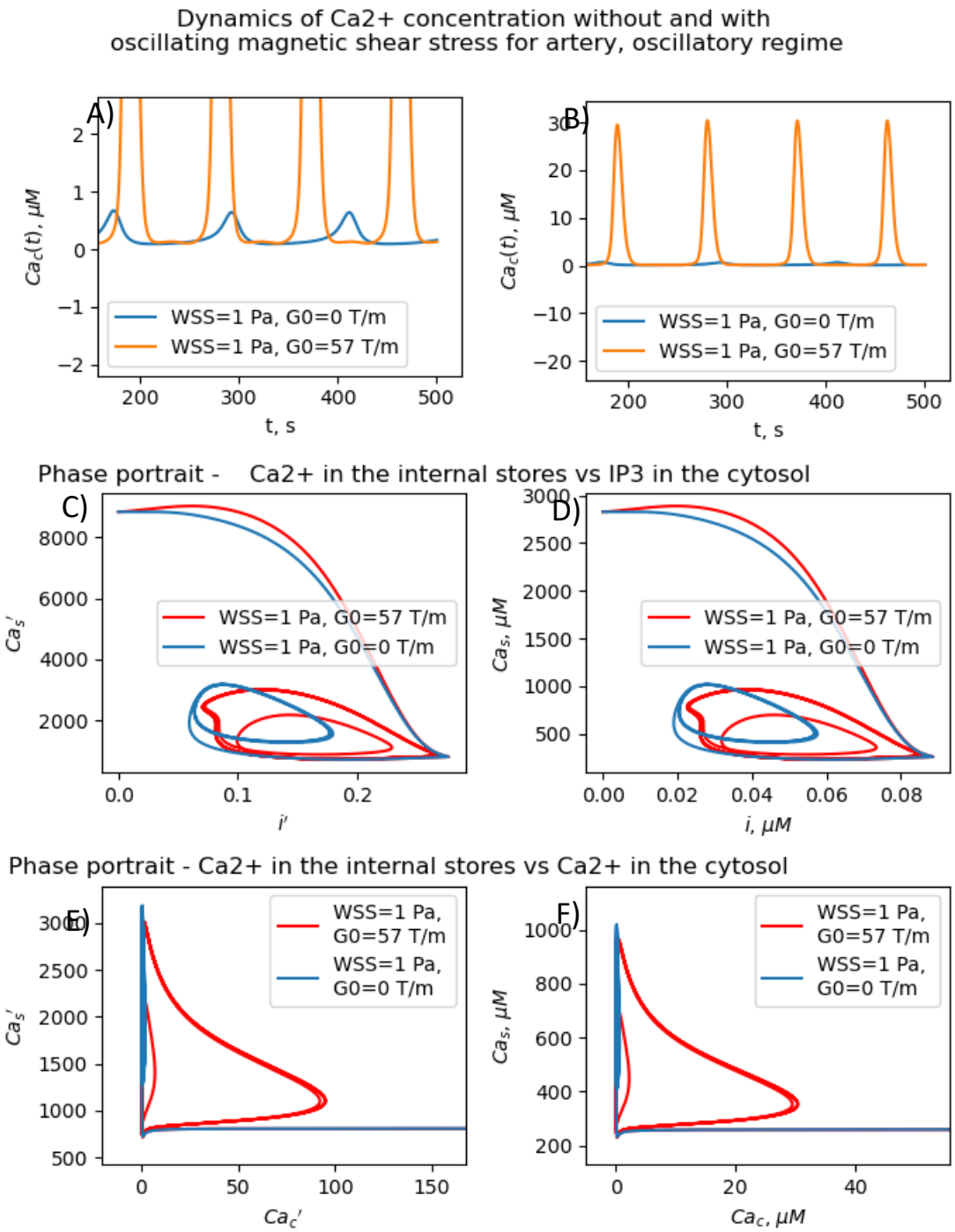


Fig. 5. Resonant-like dynamics of concentration of intracellular Ca^{2+} for artery, $m = 0.77$, $\nu = 0.011$ Hz. a) Temporary dependence of concentration of free calcium in cytosol. b) Temporary dependence of dimensionless concentration of free calcium in cytosol. c) Dependence of dimensionless concentration of calcium in internal store on dimensionless concentration of IP_3. d) Dependence of concentration of calcium

in internal store on concentration of IP_3. e) Dependence of dimensionless concentration of calcium in internal store on dimensionless concentration of free calcium in cytosol. f) Dependence of concentration of calcium in internal store on concentration of free calcium in cytosol.

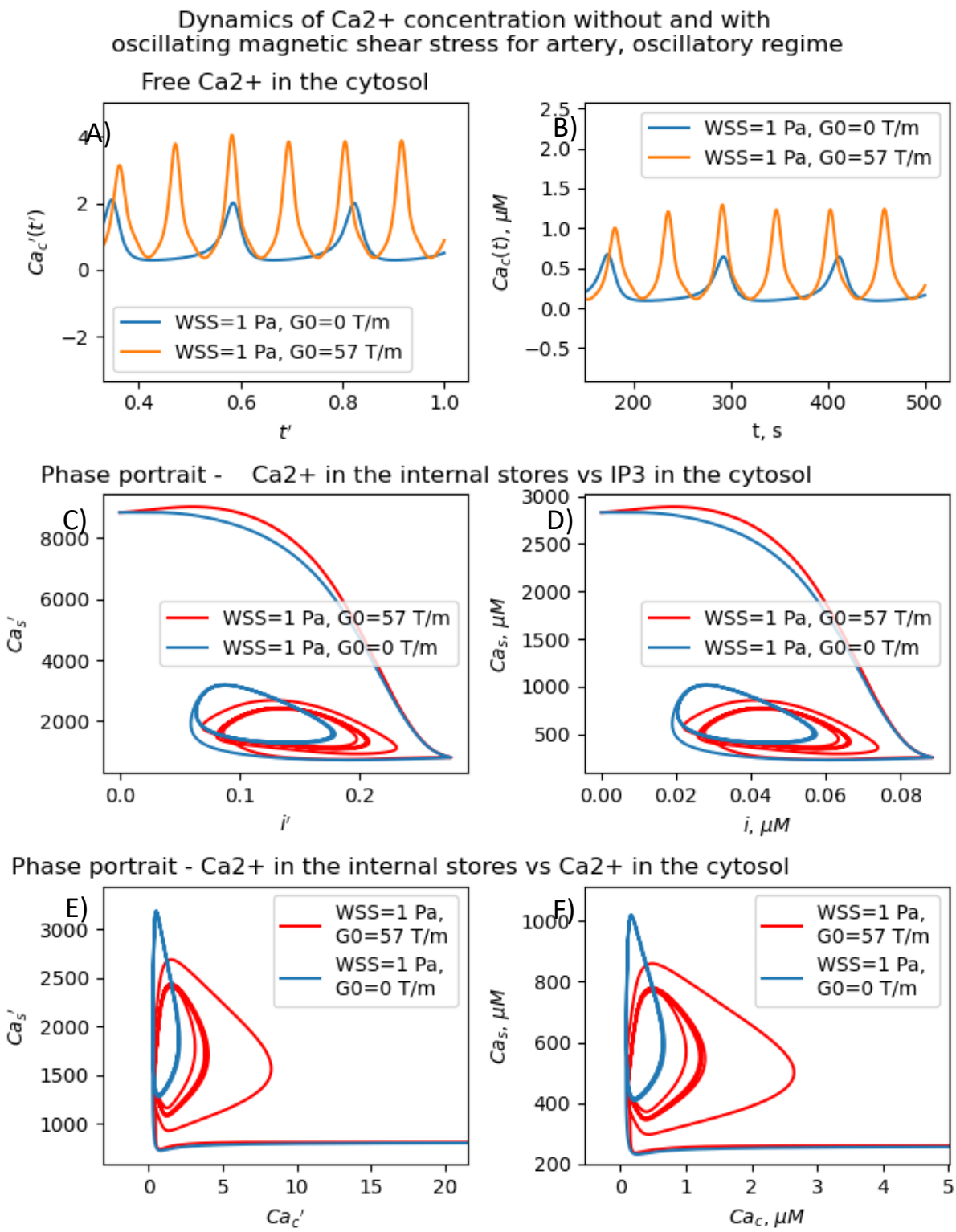


Fig. 6. Non-resonant dynamics of concentration of intracellular Ca^{2+} for artery, $m = 0.77$, $\nu = 0.018$ Hz. a) Temporary dependence of concentration of free calcium in cytosol. b) Temporary dependence of

dimensionless concentration of free calcium in cytosol. c) Dependence of dimensionless concentration of calcium in internal store on dimensionless concentration of IP_3. d) Dependence of concentration of calcium in internal store on concentration of IP_3. e) Dependence of dimensionless concentration of calcium in internal store on dimensionless concentration of free calcium in cytosol. f) Dependence of concentration of calcium in internal store on concentration of free calcium in cytosol.

As seen in Figs. 4, the MF influence on the gating of mechanosensitive Ca^{2+} ion channels and intracellular Ca dynamics is low if the first magnetic parameter $m \ll 1$. This conclusion is valid only for non-oscillatory dynamics of Ca^{2+} concentration and for oscillatory dynamics of Ca^{2+} concentration in the case when a MF frequency is high in comparison with the resonant one. For example, $m = 0.014$ where $G_0 = 1$ T/m, $r = 100$ nm, $M_s = 510 \cdot 10^3$ A/m, $P_s = 5\ Pa$. In the last case, the MF influence on the probability of opening of mechanosensitive Ca^{2+} ion channels is about 1-2% and the MF influence on the rate of intracellular Ca flux inside a cell is about 2% in comparison with the conditions without MF.

On the contrary, in the case of oscillatory Ca^{2+} concentration dynamics, even for small *m*-parameters the effects of low gradient MFs and low uniform MFs on intracellular Ca dynamics can be significant, up to tens of percent, especially when the MF frequency is much lower than the frequency of self-oscillations of Ca^{2+} concentration. Indeed, the diagrams (Fig. 4) show that a MF can change the concentration of intracellular free calcium from resting value (non-stimulating around 0.1 µM=100 nmol/L) to the level of several µM activating signaling transduction. That is why magnetic field of appropriate strength and frequency induce additional WSS and render an influence on calcium dependent processes. Here, magnetic field-amplified calcium waves represent a special interest. It is known that, in endothelial cells, Ca waves can propagate within arterial wall [83]. Since Ca waves are often initiated by intracellular release of calcium from stores such as the endoplasmic reticulum, they can be triggered by a MF in arteria with the above-mentioned values of the *m* and µ parameters. This provides an opportunity for frequency modulation of calcium waves using a magnetic field, which could enable the control of various cellular processes, including cell proliferation, differentiation,

and migration. Fig. 7 schematically demonstrates how to alter cell fate by magnetic switching of the frequency bands of calcium waves. Detailed information regarding the MF frequency bands, decoding of proteins, and metabolic pathways is provided in Table 3.

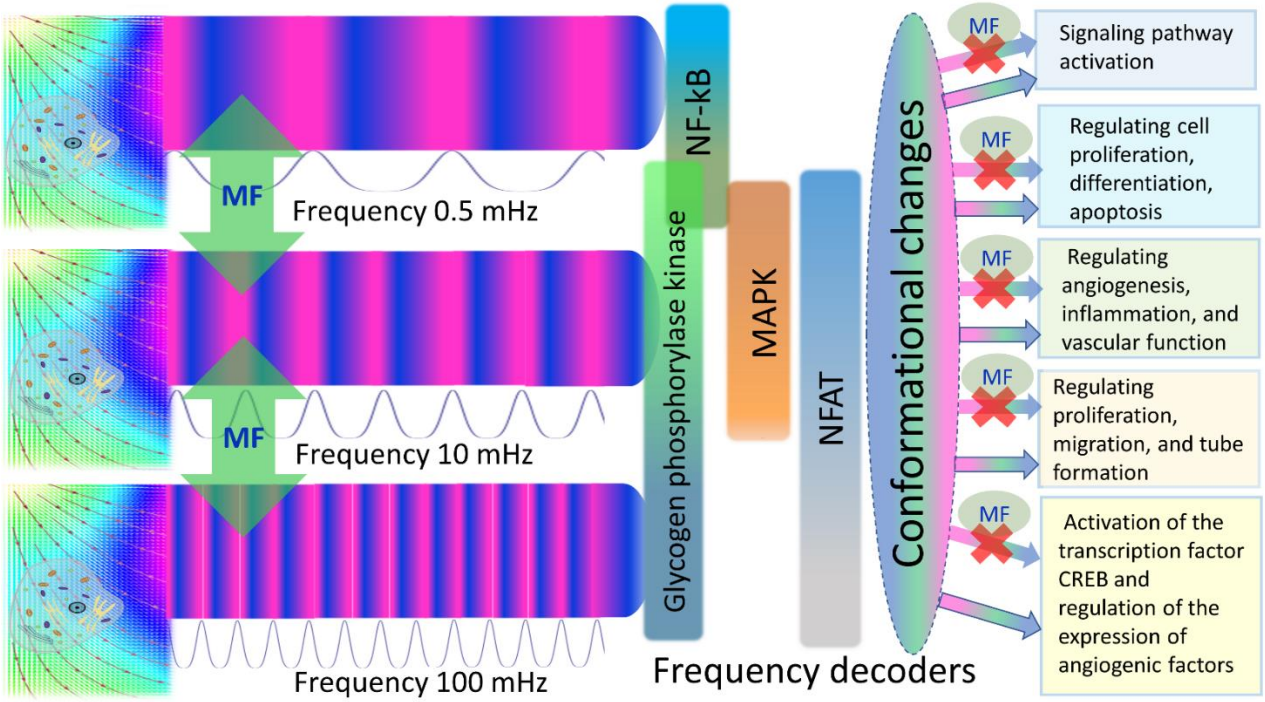


Fig. 7. Schematic model of Ca-frequency decoders and magnetic switching of metabolic pathways in endothelial cells is depicted, with four frequency decoders shown: NF-kB, MAPK, NFAT, and Glycogen phosphorylase kinase (GPK) [5]. A magnetic field (green vertical arrows and spots marked with MF) switches the frequency bands of calcium waves, thereby changing/closing enzyme activity and metabolic pathways.

Our model shows that the stable concentration of Ca^{2+} level is established not immediately but after some delay (transition processes) in the case of non-oscillatory regime of Ca^{2+} dynamics. The model also shows some delay (transition processes) in the case of oscillatory regime of Ca^{2+} dynamics. It means that some time is needed for set up of self-oscillations under magnetic field influence. The transition process is slow, the delay time is about hundreds of seconds. This prediction of the model is in agreement with observation of slow

relaxation of brain activity under influence of a magnetic field (with magnetic field flux density close to the geomagnetic field) [84], namely, alpha-power began to drop from pre-stimulus baseline levels as early as 100 ms after magnetic stimulation, decreasing by as much as 50% over several hundred milliseconds, then recovering to baseline by 1 s post-stimulus [84].

Discussion

Regulation of cell fate with magnetic fields

We suggested an approach for modulating the calcium signaling frequency using uniform and gradient magnetic fields. Our theoretical model is based on the previous experimentally verified models of calcium dynamics in endothelial cells [24,25]. The key points of our approach are the following. An externally applied MF exerts forces on biogenic and non-biogenic magnetic nanoparticles which are always present in organisms (Fig. 1). The nanoparticles transmit magnetic forces to the cell membrane, causing shear stress in cell walls, which, in turn, changes the activity of calcium ion channels and modifies the intracellular calcium pattern. The application of a time-varying magnetic field enables both frequency modulation of calcium signaling and switching between calcium decoders. From this perspective, it is believed that certain human diseases resulting from abnormal intracellular calcium levels and disruptions in calcium signaling may be treated with time-varying magnetic fields. The specific frequency and amplitude of these fields can be determined by two parameters: m and μ, which operating values are depicted in Fig. 4. Finally, the possibility of the magnetic switching between the calcium decoders (Fig. 7) opens the door for the modulation of biochemical pathways and the fate of human cells in the absence of chemical or biological agents.

Treatment of diseases with alternating magnetic fields

Since elevated calcium level stimulates endothelial proliferation [85] and promotes the growth of new vessels (angiogenesis) [85], a MF can serve as noninvasive tool for calcium level setting. In this view, static and

alternating MFs can be used for treating injuries, trauma, strokes; enhancing wound healing (if magnetic shear stress is applied along the hydrodynamic one) or for inhibiting endothelial proliferation for anticancer treatment (if magnetic shear stress is applied opposite to the hydrodynamic one. In cases when elevated calcium leads to rise of blood pressure [86], the magnetic field induced shear stress, which is parallel to hydrodynamic (blood flow), can be used for treating hypotension and magnetic shear antiparallel to blood flow, to treat hypertension. So far as an elevated calcium concentration results in increase of endothelial permeability [87], in particular, supporting transendothelial migration of immune cells [88], a MF can be utilized for immunomodulation. For example, a magnetic field generating magnetic shear stress, which opposes the hydrodynamic force, can be used to decrease endothelial permeability for immune cells. Consequently, this can inhibit inflammation and aid in the development of immunosuppressive drugs for organ transplantations, as well as the treatment of autoimmune diseases, among other applications. Moreover, calcium signaling in endothelial cells induces neuromodulation and impacts blood flow control [89]. Hence, the application of a MF shows promise for controlling neurovascular coupling and treating vascular dysfunctions associated with aging and neurodegenerative disorders. Future research in the direction of magnetic field induced wall shear stress and gating of calcium ion channels in endothelial cells opens perspective to treat cardiovascular diseases (including atherosclerosis) and cancer.

MF-assisted Ca^{2+} ion channel gating can also be utilized to induce magnetic field-assisted synchronization of calcium oscillations in all cells within a target region (organ or tissue). This approach can be used to treat diseases in which defects in this coordinating mechanism contribute to the pathology, for example, Type 2 diabetes [90].

The results of this research contribute to the targeting of ion channels, which represent the second-largest class of membrane proteins in the market after G Protein-Coupled Receptors (GPCRs) [91]. To achieve that, we propose the administration of chains of artificial and/or biogenic magnetic nanoparticles to a specific

lesion site, followed by the application of appropriate magnetic shear stress as a therapeutic method for targeting the mechanosensitive Ca^{2+} ion channels in endothelial cells.

Summarizing, our findings might pave the way for the use of oscillating and pulsed magnetic fields to improve functions of endothelial cells. The suggested model and obtained results are of great importance for further developing novel noninvasive and nondestructive physical approaches in cell therapy and medicine.

Magnetic sensing

One of the key results of our model is that the geomagnetic field can also affect calcium patterns in human organism. Indeed, a uniform MF with the magnitude of the order of the geomagnetic field (m=0.266) can influence intracellular Ca dynamics if the MF frequency is close to the frequency of Ca^{2+} self-oscillations (Fig. 4 E, F). So, in a case when $m \approx 0.27$ and the MF direction is defined by the angles $\theta = \frac{\pi}{2}$, $\gamma = \frac{\pi}{2}$, the uniform geomagnetic field of magnitude ≈ 50 μT can affect the calcium channels and neural activity. In this sense, our conclusion that the geomagnetic field (Fig. 4 E, F) enables an impact on neural activity through the modulated calcium signaling are in line with the experiments [84] revealing the sensitive of neural response to a MF of the same flux density as the geomagnetic field [84]. Moreover, [84], can be interpreted in the context of our results as follows.

The normal to the plane of membrane component of the uniform MF doesn't create the shear stress while the shear stress is created by the MF in-plane component. That is why left-right asymmetry depending on the MF direction is expected in the effects on intracellular calcium signaling if the average orientation of the membrane with chains of magnetic nanoparticles has a left-right inclination in human or animal body. The upward -downward asymmetry in the MF impacts on intracellular calcium signaling is expected if the mean orientation of the magnetization of residual nanoparticle chains has a non-zero vertical component of magnetization which usually arises due to the vertical component of the geomagnetic field (downward directed in the Northern Hemisphere). Thus, the observed in [84] asymmetry is likely because the shear stress in within arterial wall depends on the MF direction via the magnetic torque which is the cross product of two

vectors: the magnetic moment and magnetic field induction, $\boldsymbol{\tau}_{mag}=[\boldsymbol{p}\times\boldsymbol{B}]$. Because this product changes sign when the magnetic field direction changes to the opposite (that is, $\boldsymbol{B} \rightarrow -\boldsymbol{B}$), both the magnetic torque and wall shear stress reverse direction. Considering that mechanosensitive ion channels on arterial and capillary walls respond to shear stress caused by hydrodynamic blood flow (τ_h), and that magnetic torque (τ_{mag}) is another factor affecting these channels such that $\tau=\tau_h\pm\tau_{mag}$ (with 'plus' indicating the same direction for shear stresses from blood flow and magnetic torque, and 'minus' indicating opposite directions), the reason for the asymmetry in the effects of upward and downward magnetic fields becomes clear. Indeed, for example, let the downward MF generate shear stress coinciding with the direction of blood flow, $\tau=\tau_h+\tau_{mag}$. In this case, the downward MF opens more mechanosensitive ion channels than the upward MF for which stress is $\tau=\tau_h-\tau_{mag}$. Thus, the opposite directions of a MF of the same magnitude can lead to quite different calcium patters and thereby cause different neural responses.

That is why the results of [84] about right-left and up-down symmetry breaking and disappearance of magnetic field effects can be in accordance with the results of present research. We hope that our findings represent one more step toward understanding the process of signal transduction in the human body in response to weak magnetic field influences and magnetic sensing.

Possible hidden mechanisms of biomagnetic effects

Thousand papers dealing with study of biomagnetic effects of low and moderate MFs do not pay attention to a possible presence of biogenic and residual artificial magnetic nanoparticles in organisms, in particular, in endothelial cells [41,92–94]. Nevertheless, as above discussed such nanomagnets are the active targets of static and especially low-frequency oscillating and rotating MFs. In this view, the above suggested physical mechanism and model of the magnetic field impacts on the calcium patterns and signaling in endothelial cells can play a hitherto unexpected role in creating physiological responses of organisms to externally applied MFs. The range of individual responses may be partially attributed to diversity in nanoparticles number and their localization rather than to other underlying processing.

Prospects for experiments

Future experiments should examine how static and alternating MFs interact with other ion channels on cell membranes bound to biogenic and artificial residual magnetic nanoparticles to determine mechanical stresses and mechanisms of changing cell machinery. Future studies should also examine differences in responsiveness of different cell types to magnetic fields and signal processing. It is also highly desirable to develop theoretical models to investigate the effects of magnetic fields on calcium dynamics in other cell types, especially MF impact on calcium signaling in brain neurons. We hope that our study provides a roadmap for future studies aiming to replicate and extend research into magnetobiology.

Materials and methods

Model

Plank's model [24] of intracellular calcium dynamics was generalized, taking into account the wall shear stress (WSS) induced by a gradient or uniform magnetic field, as well as a static or oscillating magnetic field. This was achieved by considering the magnetic field's influence on biogenic and/or artificial magnetic nanoparticles embedded in the cell membrane of endothelial cells. The WSS induced by a gradient or uniform magnetic field is calculated according to formulas (5) and (6). The MF-induced WSS changes the probability of Ca^{2+} mechanosensitive channel opening and the rate of Ca^{2+} flux inside the cell according to formulas (2) and (4), respectively.

The main equations, notions and terms

The Plank's model of Ca^{2+} dynamics considers 4 dynamic variables: concentrations of IP3 in the cytosol, free Ca^{2+} in the cytosol, buffered Ca^{2+} in the cytosol, Ca^{2+} in the internal stores. For an endothelial cell the scheme of Ca^{2+} fluxes is shown in Fig. 2. The numerical values of the dynamic variables of the model of Ca^{2+} dynamics

are collected in Table 1 and Table S1. In Fig. 2, the rates of Ca^{2+} fluxes (Table 2) are schematically presented for endothelial cells in a modified Plank's model taking into account MF-induced WSS.

Table 1. Dynamic variables in the modified Plank's model for calcium dynamics taking on account WSS induced by magnetic field.

Dynamic variable	Dimensional notation
Concentrations of IP3 in the cytosol	i
Free Ca^{2+} in the cytosol	$Ca_c, \mu M$
Buffered Ca^{2+} in the cytosol	$Ca_b, \mu M$
Ca^{2+} in the internal stores	$Ca_s, \mu M$
Sum of free Ca^{2+} in the cytosol and buffered Ca^{2+} in the cytosol	$Ca_t = Ca_c + Ca_b, \mu M$

Table 2. Fluxes in the modified Plank's model for calcium dynamics taking on account WSS induced by magnetic field. The parameters in the second column are represented in Table S2.

Flux	Formular
Rate of release of Ca^{2+} from the endoplasmic reticulum (ER)	$q_{rel} = k_3 \frac{Ca_c}{K_{CICR} + Ca_c} \left(\frac{i}{K_2 + i}\right)^3 Ca_s$
Rate of resequestration of Ca^{2+} back into the ER	$q_{res} = k_4 \left(\frac{Ca_c}{K_3 + Ca_c}\right)^2 - k_5 Ca_s^2$

Rate of influx that contribute to the free cytosolic Ca^{2+}	$q_{in} = k_{CCE}(Ca_{s,0} - Ca_s)(Ca_{ex} - Ca_c) + \frac{q_{\max}}{1 + \alpha \exp\left(-\frac{f_e\left(W(\tau + \tau_{magn})\right)}{kT_eN}\right)}$
Rate of efflux	$q_{out} = \frac{k_8}{K_4 + Ca_c}$
'On' rate of cytosolic buffering	$q_{on} = k_6 Ca_c(B_T - Ca_b)$
'Off' rate of cytosolic buffering	$q_{off} = k_7 Ca_b$
Dynamic equilibrium condition for cytosolic buffering	$q_{on} = q_{off}$

The system of equations for modelling calcium dynamics [24] for the dynamic variables represented in Table 1:

$$\frac{di}{dt} = k_1 \frac{\phi}{K_c + \phi} \cdot \frac{Ca_c}{K_1 + Ca_c} - k_2 i \tag{10}$$

$$\frac{dCa_c}{dt} = q_{rel} - q_{res} + q_{in} - q_{out} - q_{on} + q_{off} \tag{11}$$

$$\frac{dCa_b}{dt} = q_{on} - q_{off} \tag{12}$$

$$\frac{dCa_s}{dt} = -V_r(q_{rel} - q_{res}) \tag{13}$$

Note that in Eqs. 10 and 11, there is one parameter, q_{in}, which is dependent on the magnetic field through the wall shear stress. The variables, rates and parameters in the right parts of (10)-(13) are represented in Table 1, Table 2, Table S1, and Table S2. See Supplemental Material at [URL will be inserted by publisher] for the transformation of the system of equations (10)-(13) to the dimensionless form.

The following parameters of Ca^{2+} oscillatory dynamic pattern are important for decoding and transmission of cell signal [5]:

1) The period of Ca^{2+} oscillations T_{Ca_c} and the corresponding frequency of Ca^{2+} oscillations $\nu_{Ca_c} = \frac{1}{T_{Ca_c}}$. If the oscillation frequency is much lower than the typical working on-off-frequency of the specific decoding enzyme then no correct signal is transmitted [5].

2) The spike duration which is calculated as full duration half maximum (FDHM) [5]. The cumulative Ca^{2+} spike duration conveys information [95]. When the frequency is kept constant, the spike duration varies; the cumulated spike duration also changes as the cell employs pure frequency encoding [96].

3) The duty cycle. The duty cycle is the ratio of the spike duration to the period of oscillations. Maximum frequency sensitivity is observed for signals with duty cycles between 0 and 0.5 [5].

4) The amplitude of the spike [5]. The silent free calcium concentration is about 100 nmol/L in resting (non-stimulated) cells, an increase in intracellular free calcium in the form of sequence of spikes up to about 1 µmol/L is the key signal to activate the cells [97].

Synchronization index [90]. It characterizes the degree of synchronicity of calcium oscillations according to the methodology from the reference [90]. For example, individual mouse pancreatic islets exhibit oscillations in $[Ca^{2+}]i$ and insulin secretion in response to glucose *in vitro*, the oscillations of a million islets are coordinated within the human pancreas *in vivo* [90]. Islet to islet synchronization is necessary for the pancreas to produce regular pulses of insulin. Defects in this coordinating mechanism could contribute to the disrupted insulin secretion observed in Type 2 diabetes [90].

In a general case, the magnetic field frequency doesn't coincide with the frequency of self-oscillations of the free cytosolic Ca^{2+} concentration. That is why the temporary pattern of spikes becomes quasiperiodic and additional spikes appear with amplitude increasing with increase of parameter m. The appearance of additional spike with infinitesimal amplitude (which increases as the magnetic field increases) is the reason

of “foam-like” region in the last row of images in Fig. 4. This “foam-like” region separates the region of low WSS induced by magnetic field from the region of moderate WSS induced by magnetic field. The region of low WSS induced by magnetic field is characterized by the periodic pattern of spikes with the frequency of self-oscillations in Plank’s model. While the region of moderate WSS induced by magnetic field is characterized by quasiperiodic pattern of spikes of free intracellular Ca^{2+} concentration. The quasi-periodicity of spike’s pattern is imposed by both the frequency of self-oscillations and magnetic field frequency.

Two regimes of dynamics of concentration of free intracellular calcium are modelled: non-oscillating (the parameters for non-oscillating regime are represented in the column 4 in Table S2) and oscillating (the parameters for oscillating regime are represented in the column 5 in Table S2). The following parameters of Ca^{2+} oscillatory dynamic pattern are calculated after passing the transition process on the basis of solving the set of differential equations (10) – (13) for oscillatory regime (see the list of parameters of Plank’s model in Table S2):

- the time averaged quasi-period of oscillations of free cytosolic Ca^{2+} concentration $\langle T_{Ca_c} \rangle$ and the corresponding time averaged quasi-frequency of oscillations of free cytosolic Ca2+ concentration $\langle \nu_{Ca_c} \rangle = \frac{1}{\langle T_{Ca_c} \rangle}$. The quasi-period of quasiperiodic oscillation of intracellular calcium characterizes the time interval between the neighboring spikes of free cytosolic Ca^{2+} concentration. The quasi-period $\langle T_{Ca_c} \rangle$ is calculated as twice of the average time interval between the neighboring maxima and minima in time-dependent solution of the differential equations (10)-(13). The initial transition process is excluded from averaging.
- the time averaged amplitude of the spike of free cytosolic Ca^{2+} concentration $\left\langle Ca_c^{(ampl)} \right\rangle$. The average amplitude of spike of intracellular free cytosolic Ca^{2+} concentration is calculated as the half of the time averaged absolute value of the difference between calcium concentration in maxima (minima). The amplitudes of at least 20 maxima and minima are averaged for oscillatory regime. The initial transition process is excluded from averaging.

- the maximum amplitude of the spike of free cytosolic Ca^{2+} concentration $\left\langle Ca_c^{(max)} \right\rangle$. The initial transition process is excluded from calculation of the maximum amplitude.

All the calculations were carried out for over 20 quasi-periods of oscillation of the dynamic variable for oscillatory regime (see the list of parameters of Plank's model in Table S2). Ten initial quasi-periods of oscillation of dynamic variable are excluded from calculations to exclude the transition processes passing before the oscillating regime approaches the stable periodic orbit. The amplitudes of excluded initial periods are sensitive to the initial conditions for the dynamic variables. Such approach results in the amplitudes and frequencies that are not sensitive to the initial conditions. The notation $\nu = \frac{\omega}{2\pi}$ is used to define the frequency of oscillation of external magnetic field.

The exclusion of the transition process from the analysis of free calcium concentration dynamics in oscillating regime helps to exclude from the analysis the data that are very sensitive to the initial conditions for the dynamic variables of the model. Thus, the exclusion of the transition process from the analysis of free calcium concentration dynamics helps to analyze stable regimes of dynamics free calcium concentration which can be settled due to long-lasting magnetic field influence. That is why the results of the paper don't include the analysis of the influence of single short magnetic field impulse on the dynamics of free calcium concentration. In other words, there is a spike, which we manually cut off using the code written on python programming language, excluding the time range from t = 0 to the duration of the transition process. Then self-oscillations are set if the model parameters are taken for oscillatory regime.

The following parameters of Ca^{2+} non-oscillatory dynamic pattern (see the list of parameters of Plank's model in Table S2) are calculated on the basis of solving the set of differential equations (10) – (13):

- the time averaged intracellular free calcium concentration $\langle Ca_c \rangle$. The initial transition process is not excluded from averaging.

- the time averaged standard deviation of the free calcium concentration for non-oscillatory regime $\left\langle Ca_c^{(std)} \right\rangle$. The initial transition process is not excluded from averaging; the transition process characterized by the initial spike of calcium concentration.

Computational simulations

The results of numeric solving of equations (10-13) of intracellular calcium dynamics were carried out using python programming language, numpy and scipy packages.

Bioinformatic analysis

The metabolic pathways of calcium decoding proteins in endothelial cells, diseases related to dysregulation of these pathway and drug targets were analyzed because magnetic field can control both the frequency and amplitude modulation of calcium signal. Search tools in bioinformatic databases (KEGG) and literature data mining were used for this purpose.

Table 3. Magnetic field influence on decoding free intracellular calcium signals in endothelial cells.

Decoding protein • Metabolic pathway / Description • Diseases related to dysregulation of the pathway, drug targets	Frequency range for effective decoding / Duty cycle range for effective decoding • optimal frequency / optimal duty cycle • Magnetic field effects
MAPK (mitogen-activated protein kinase), mitogen-activated protein kinase 4 (Map4k4)	• 1.7–17 mHz / • 0.085–0.85 •

• MAPK signaling pathway / The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway) is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. The signal starts when a signaling molecule binds to the receptor on the cell surface and ends when the DNA in the nucleus expresses a protein and produces some change in the cell, such as cell division. The pathway includes many proteins, such as mitogen-activated protein kinases (MAPKs), originally called extracellular signal-regulated kinases (ERKs), which communicate by adding phosphate groups to a neighboring protein (phosphorylating it), thereby acting as an "on" or "off" switch. MAPK or MAP kinase is a type of protein kinase that is specific to the amino acids serine and threonine (i.e., a serine/threonine-specific protein kinase) [98]. MAPKs are involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock and proinflammatory cytokines [98]. They regulate	

cell functions including proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis. MAP kinases are found in eukaryotes only, but they are fairly diverse and encountered in all animals, fungi and plants, and even in an array of unicellular eukaryotes [98]. • When one of the proteins in the pathway is mutated, it can become stuck in the "on" or "off" position, a necessary step in the **development of many cancers**. Components of the MAPK/ERK pathway were first discovered in cancer cells, and drugs that reverse the "on" or "off" switch are being investigated as cancer treatments. Constitutive loss of endothelial cell Map4k4 in mice causes postnatal lethality due to **chylothorax**, suggesting that Map4k4 is required for normal lymphatic vascular function [99]. Mice constitutively lacking EC Map4k4 displayed **dilated lymphatic capillaries, insufficient lymphatic valves, and impaired lymphatic flow** [99]; furthermore, primary endothelial cells derived from these	

animals displayed enhanced proliferation compared with controls [99].	
NF-κB (NFKB in KEGG - nuclear factor NF-kappa-B; nuclear factor kappa-light-chain-enhancer of activated B cells) • The Nuclear Factor NF-κB Pathway / The nuclear factor NF-κB pathway has long been considered a prototypical proinflammatory signaling pathway, largely based on the role of NF-κB in the expression of proinflammatory genes including cytokines, chemokines, and adhesion molecules. NF-κB is a protein complex that controls transcription of DNA, cytokine production and cell survival [100–102]. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation and bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection. NF-kB target genes could be classified in different functional groups [100]. Those with a primarily inflammatory function were predominant [100]. NF-kB controls the	1) 0.56–10 mHz / 0.028–0.5 2) 0.56 mHz / 0.8–0.9 • 10 mHz

global pro-inflammatory response in endothelial cells [100]. Genetic evidence in mice has revealed complex roles for the NF-kB in inflammation that suggest both pro- and anti-inflammatory roles for this pathway. NF-κB has also been implicated in processes of synaptic plasticity and memory. • Incorrect regulation of NF-κB has been linked to **cancer**, **inflammatory** and **autoimmune diseases**, **septic shock**, **viral infection**, and **improper immune development**. NF-kB has long been considered as a **target for new anti-inflammatory drugs** [102]; however, these recent studies suggest this pathway may prove a difficult **target in the treatment of chronic disease** [100,102]. Deregulated NF-κB activation contributes to the pathogenic processes of **various inflammatory diseases** [103].	
NFAT (Nuclear Factor of Activated T-Cells) • Calcium–Calcineurin–NFAT Signaling Pathway; Ca^{2+}/nuclear factor of activated T-cells (Ca^{2+}/NFAT) signaling pathway / NFAT signaling plays a key role in angiogenic cell behaviors.	1) 2.5–10 mHz / 0.125–0.5 2) 2 – 33 / 0.04–0.66 3) 16.7 mHz / 0.33 • 20 mHz / 0.2–0.3

NFAT is a family of transcription factors shown to be important in immune response [104]. One or more members of the NFAT family is expressed in most cells of the immune system. NFAT is also involved in the development of cardiac, skeletal muscle, and nervous systems [104]. NFAT was first discovered as an activator for the transcription of IL-2 in T cells (as a regulator of T cell immune response) but has since been found to play an important role in regulating many more body systems [104]. NFAT-mediated gene upregulations lead to well-known T cell differentiations and activation, but most recently, many reports also showed the NFAT activity correlates with innate immune cell activation, bone metabolism, angiogenesis, and tissue regenerations [105]. In the vascular system NFAT (including the isoforms c1 and c3) contributes to cell growth, remodeling of smooth muscle cells, controls vascular development and angiogenesis and is activated in response to inflammatory processes and high intravascular pressure [106]. In the endothelium, NFAT	

controls gene expression during remodeling and is activated by growth factors or histamine [106]. • NFAT transcription factors are involved in many normal body processes as well as in development of several diseases, such as **Kawasaki disease**, **inflammatory bowel diseases** and **several types of cancer**. NFAT is also being investigated as a **drug target for several different disorders** [104]. NFAT signalling is a pharmacological **target for the induction of immunosuppression**. Proteins of the NFAT family are Ca^{2+}-sensitive transcription factors, which are involved in **hypertrophic cardiovascular remodeling** [106]. NFAT signaling promoted the **inflammation of wounds** [105]. Calcineurin-NFAT inhibitor, cyclosporine A (CsA), is the most famous **immunosuppressive drug after organ transplantations** [105].	
GP (Glycogen phosphorylase) • glycogenolysis pathway [106] / Glycogen phosphorylase catalyzes the rate-limiting step in glycogenolysis in animals by releasing	1.7–170 mHz /

glucose-1-phosphate from the terminal alpha-1,4-glycosidic bond. Glycogen phosphorylase is also studied as a model protein regulated by both reversible phosphorylation and allosteric effects. GP is an allosteric enzyme and with seven different binding sites discovered to date, there are multiple opportunities for modulation of its activity. • The inhibition of glycogen phosphorylase has been proposed as one method for **treating type 2 diabetes**. Glycogen phosphorylase is an important therapeutic **target for type 2 diabetes** having a direct influence on blood glucose levels through the glycogenolysis pathway. Considerable efforts toward the design of **drug-like GP inhibitors** have taken place in recent years. Many of these inhibitors are natural products and their analogues.	

Acknowledgements

The project is partially funded from the Mobility Program budget of the Czech Academy of Sciences and Chinese Academy of Sciences (CAS-23-01). The authors would like to thank Prof. Xin Zhang for the fruitful discussions.

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Notes

See Supplemental Material at [URL will be inserted by publisher] for the open access python code as .zip file containing the python project *MagniCa*.

Author contributions:

O.G. problem statement, analytical calculations and numeric simulation, writing python code, literature data mining, developing conclusions; S.G. problem statement, numeric simulation, writing python code, literature data mining, developing conclusions; T.P. analytical calculations, literature data mining, developing conclusions; V.Z. problem statement, analytical calculations, literature data mining, developing conclusions.

Competing interests:

No conflict of interest