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Application of Pulsed Magnetic Ponderomotive Force for Intra-Cellular Gene Delivery

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Abstract—A novel method of the aerosolized gene delivery is proposed, and its feasibility is computationally analyzed. Aerosolized DNA or siRNA attached to magnetic particles can be accelerated using ponderomotive force to high velocities in a pulsed magnetic field of a solenoid and efficiently delivered to cell culture or to the lung epithelium. The proposed noninvasive method of intra-cellular gene delivery can be considered as a combination of principles of classical high-pressure air jet gene delivery with magnetophoresis.

1. INTRODUCTION

Magnetic field based drug delivery methods are one of the most attractive approaches for localizing drug in the body, because magnetic forces act at relatively long range and do not affect most of biological tissues. Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, such as a tumour, without any toxic effects to normal adjacent tissue or to the whole body [1–16].

In magnetic targeting, a drug, gene, or therapeutic radioisotope is bound to a magnetic compound, injected into a patients blood stream, and then stopped with a powerful magnetic field in the target area. Depending on the type of drug, it is then slowly released from the magnetic carriers (e.g., release of chemotherapeutic drugs from magnetic micro-spheres) or confers a local effect (e.g., irradiation from radioactive microspheres; hyperthermia with magnetic nanoparticles). It is thus possible to replace large amounts of freely circulating drug with much lower amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several-fold increased localized drug levels.

Aerosolization therapy for lung diseases has been applied for a long time [17–22]. However, it has now become clear that the lung is a perfect point of entry not only for local therapy, but also for the systemic delivery of therapeutic substances. It provides a surface area of $100\,\mathrm{m}^2$ and is separated from the pulmonary capillary blood by a barrier of less than $1\,\mu\mathrm{m}$. Furthermore, there is no "first pass effect", as is found in the intestinal tract. Recent technical improvements, with regard to both the production and the delivery of aerosols, indicate that the development of appropriate inhalation techniques may be the therapeutic way forward for a variety of diseases. Cystic fibrosis is a particularly inviting target for aerosolized gene therapy, as it is a single-gene disease and the critical target cells, airway epithelial cells, are directly accessible to the environment. However, achieving genetic correction by airway administration of vectors has proven to be difficult. Thus, higher doses of drugs can be delivered to a cancerous lung region together with reduced side-effects in unaffected lung tissue. Recently, magnetic aerosol drug targeting was applied successfully in a various models [23–32].

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Another physical method for intra-cellular gene delivery is high-pressure air jet gene delivery that uses micron-size carrier particles made of a heavy metal (tungsten or gold) that are coated with plasmids, RNA, or dye, accelerated to a high speed using a pneumatic gas jet and launched into a biological target. A small bead penetrates cells without damaging them, gets stuck in a cell in an internal layer of the targeted tissue, and releases into the cells the gene that it carries [33–36].

Our aim in this study is to study possibility of using pulsed magnetic field instead of gas jet for acceleration of gene attached to magnetic microparticles to high velocities in analogy with high pressure air jet gene delivery method. The method of magnetic acceleration of milligram to gram size iron pellets to hypervelocities, i.e., to 10–100 km/s has been already used for the purposes of micrometeorite impact studies, terminal ballistic, and nuclear fusion [37–39].

2. COMPUTATIONAL METHODS

The differential equation governing the motion of a spherical particle with nonzero magnetic moment, $\vec{\mu}_p$, and mass, m_p, subjected to gravity field with gravitational acceleration, $\vec{g}$, and external magnetic field with flux density, $\vec{B}$, is [5–8, 40]

$$m_p \frac{\mathrm{d}\vec{v}_p}{\mathrm{d}t} = \vec{F}_D + (\vec{\mu}_p \cdot \nabla)\,\vec{B} + m_p\vec{g} + \vec{F}_{Br}, \tag{1}$$

where $\vec{v}_p$ is the particle velocity, and $\vec{F}_D$ and $\vec{F}_{Br}$ are the respective drag and stochastic Brownian forces exerted on the particle. Henceforth, we focus on the deterministic effects of magnetic targeting and viscous drag and neglect the sedimentation and stochastic Brownian forces.

Increasing magnetic field intensity causes reorientation of magnetic moments of particles domains in paramagnetic magnetite particle into external magnetic field direction. The magnetic field with sufficient magnitude (i.e., magnetic field intensity that correspond to magnetic induction in vacuum or air about $B > 500\,\mathrm{mT}$) leads to their full reorientation in one direction, and full magnetic saturation. Therefore, if we consider magnetic field strong enough to magnetically saturate particles, magnetic force on saturated particle could be described as

$$\vec{F}_M = |\vec{\mu}_p| \left(\frac{\vec{B}}{B} \cdot \nabla \right) \vec{B}, \tag{2}$$

where $|\vec{\mu}_p|$ is a magnitude of particles total magnetic moment, and the motion of particle is affected only with the external magnetic field with magnetic flux density gradient, $\vec{G}_M = ((\vec{B}/B) \cdot \nabla)\vec{B}$.

The drag force exerted on spherical particle suspended in Stokesian flow field (Reynolds number is low, i.e., $\mathrm{Re} \ll 1$) is given as

$$\vec{F}_D = 3\pi\eta_f D_p \left(\vec{v}_f - \vec{v}_p\right)_{CV} / C, \tag{3}$$

where η_f is the air dynamic viscosity ($18.6\,\mu\mathrm{Pa}\cdot\mathrm{s}$ at 30°C), the suffix CV stands for evaluation of the airflow at the particles center of volume, and C is the slip correction factor for very small particles, i.e., less than 1 μm in diameter (e.g., for particles 0.5 and 1.0 μm in diameter is 1.324 and 1.164, respectively), but for bigger particles approaches to one. Also, in our approach, we consider static velocity flow field of air ambient, i.e., $\vec{v}_f$ equals zero in whole area of interest, what yields $\vec{F}_D = -3\pi\eta_f D_p \vec{v}_{pCV}/C$.

After consideration of all mentioned assumptions, the system of ordinary differential equations (ODEs) governing motion of magnetic particle bigger than 1 μm in diameter in gradient magnetic field and Stokesian viscous flow fluid, suitable for MATLAB ODEs solver syntax notation

$$\frac{\mathrm{d}\vec{r}_p}{\mathrm{d}t} = \vec{v}_p, \qquad \frac{\mathrm{d}\vec{v}_p}{\mathrm{d}t} = \left[|\vec{\mu}_p| \left(\frac{\vec{B}(\vec{r}_p)}{B(\vec{r}_p)} \cdot \nabla \right) \vec{B}(\vec{r}_p) - 3\pi\eta_f D_p \vec{v}_p \right] / m_p, \tag{4}$$

where magnetic induction $\vec{B}$, is a function of particle position in the area of interest.

For evaluation of magnetic forces contribution due to presence of gradient magnetic field source to whole force exerted on particle it is necessary to know the external magnetic induction distribution, B. Analytically it is possible only for simple sources of magnetic field, therefore we

have used for description of our magnetic fields sources numerical method known as finite element analysis and FEMM v.4.2 (Finite Element Method Magnetics, by David Meeker, available ON-LINE: "http://www.femm.info/wiki/HomePage") software as free toolbox for MATLAB.

3. RESULTS

As a source of gradient magnetic field in proposed method using ponderomotive force for *in vitro* intracellular gene delivery in Petri dish and non-invasive *in vivo* gene delivery into the lung (we have used smaller dimensions of infant lungs in our simulations, for the reason that it is more easily realized technically) we have modeled two coils with geometric and physical parameters specified in the Table 1, tagged as hand-hold coil and coil for infant lungs, respectively. The distribution of magnetic induction for both coils is shown in Fig. 1. In present, considered currents driving magnetic field around coils are too high for practical realization, with the exception of pulsing mode, but still with high temperature generation. Although, for demonstration of idea of using ponderomotive force for gene delivery in target Petri dish or acceleration of bolus of magnetically labeled targeting compounds to the lungs, are convenient.

Both coils have been modeled using finite element method (FEM) in planar magnetostatic approximation [5], i.e., with constant driving current, as axisymmetric model and used for further calculation as 2D planar model in longitudinal axial cross-section of coil (see Fig. 1). For numerical error reduction during particle's trajectory evaluation in simulations in relatively large area of interest, it has been necessary to generate FEM model with relatively small maximal element size. We have chosen maximal element size in paraxial area of coils (area of interest), in axisymmetric model, 10 and 50 μm for hand-hold coil and coil for infant lungs, respectively, what has led to relatively high number

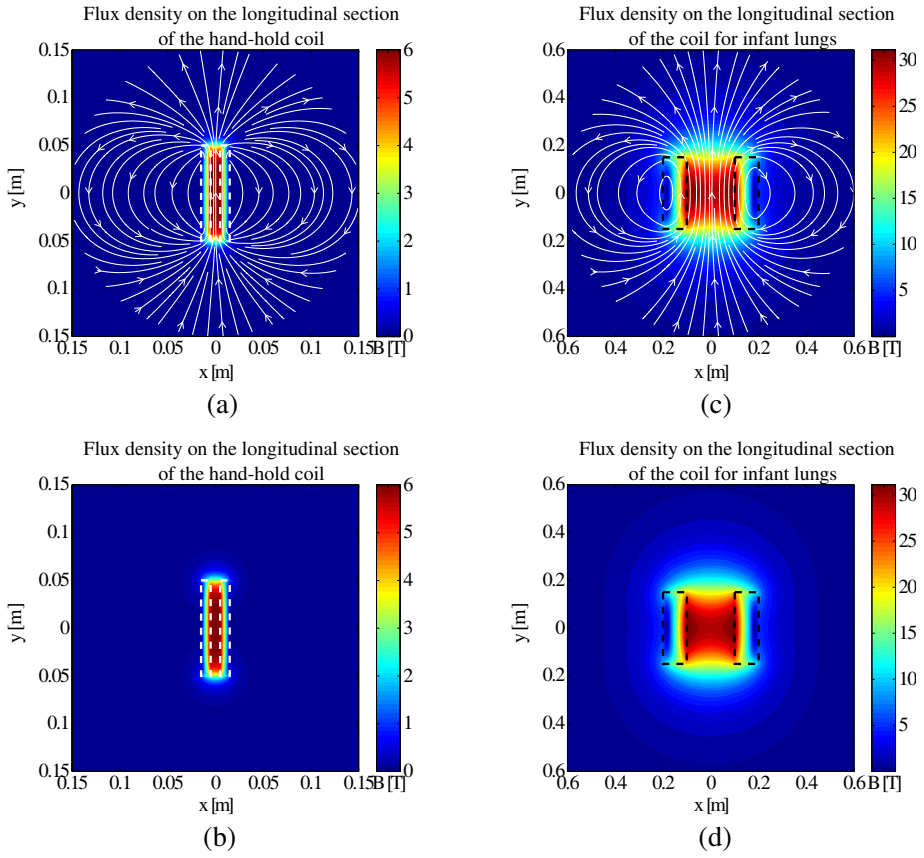

Figure 1. Distribution of magnetic induction in the longitudinal section of the hand-hold coil and coil for transfection of infant lungs, with and without streamlines.

Table 1. Parameters of coils as magnetic field sources used in simulations.

Quantity	Hand-hold coil	Coil for infant lungs
inner diameter (cm)	1	20
outer diameter (cm)	3	40
height (cm)	10	30
diameter of wire (mm)	0.46	0.46
number of turns	5 000	100 000
driving current (A)	100	100

of elements, over 7×10^6 in both cases, and therefore also to high memory requirements during both, FEM model generating and simulations accomplishment, however still realizable.

As particles for magnetic acceleration by coils in simulations we have chosen spheres 10 μm in diameter of magnetite with mass density $5000\,\mathrm{kg/m^3}$ and saturation magnetization 478 kA/m what corresponds to magnetic moment $250 \times 10^{-12}\,\mathrm{A \cdot m^2}$. Properties of fully magnetically saturated particles important for computational modeling you can find in Table 2. Chosen particle specifications are almost comparable with commercially available magnetic microparticles (e.g., from micromod Partikeltechnologie GmbH, or Chemicell GmbH).

Table 2. Parameters of particles used in simulations.

Quantity	Magnetite sphere
diameter, D_p (μm)	10
mass, m_p (kg)	2.6×10^{-12}
magnetic moment, $\lvert\vec{\mu}_p\rvert$ ($\mathrm{A \cdot m^2}$)	250×10^{-12}

We have studied motion of magnetically saturated spherical particles with magnetic moment in gradient magnetic field by realization of simulations. As primary software for trajectory computation we have used MATLAB R2013a (The Mathworks, Inc.), particularly `ode15s` solver as a tool for solving of stiff systems of ordinary differential equations based on the numerical differentiation formulas [41]. Trajectories of particles have been evaluated for each particle as a single particle problem described with ODEs (4) with equally spaced initial position in the paraxial inlet area of each coil located on axial longitudinal section of the coils. Magnetic flux density distribution around coils, $\vec{B}$, that appears in ODEs (4) describing particle's motion has been extracted during the simulation directly from the FEMM v.4.2 which communicates with MATLAB using MATLAB built in ActiveX support. Partial differentiation of magnetic flux density in gradient expression $\vec{G}_M$ in each queried point during the simulation execution has been evaluated numerically by differentiation of magnetic flux density's values in points in close proximity of queried point separated with distance $\Delta r = 1\,\mu\mathrm{m}$.

4. DISCUSSION

From the snapshots of particles movement, with initial position equally spaced in the inlet of hand-hold coil (Fig. 2) and infant lungs coil (Fig. 3) in the generated magnetic field, we can conclude that our hypothesis about the possibility of using pulsed magnetic field as a driving force for intra-cellular gene delivery is feasible and we hope that our approach would be experimentally realized in the close future both *in vitro* as well as *in vivo*, e.g., for gene therapy of cystic fibrosis in infant lungs.

As has been noted, in our present analysis we neglect the stochastic Brownian force exerted on a moving particle, whose influence relative to the gravity force, especially for particles bigger than 1 μm in diameter used in this work, is negligible as has been shown for instance in paper [42]. This effect is even considerable for a particles with higher mass density, as it is in case of magnetite's spheres. Magnetic force on particles due to modeled external gradient magnetic fields, whose magnetic induction gradient (in the area of interest) is in a range 10–150 T/m in the case of coil for infant lungs or even reaches

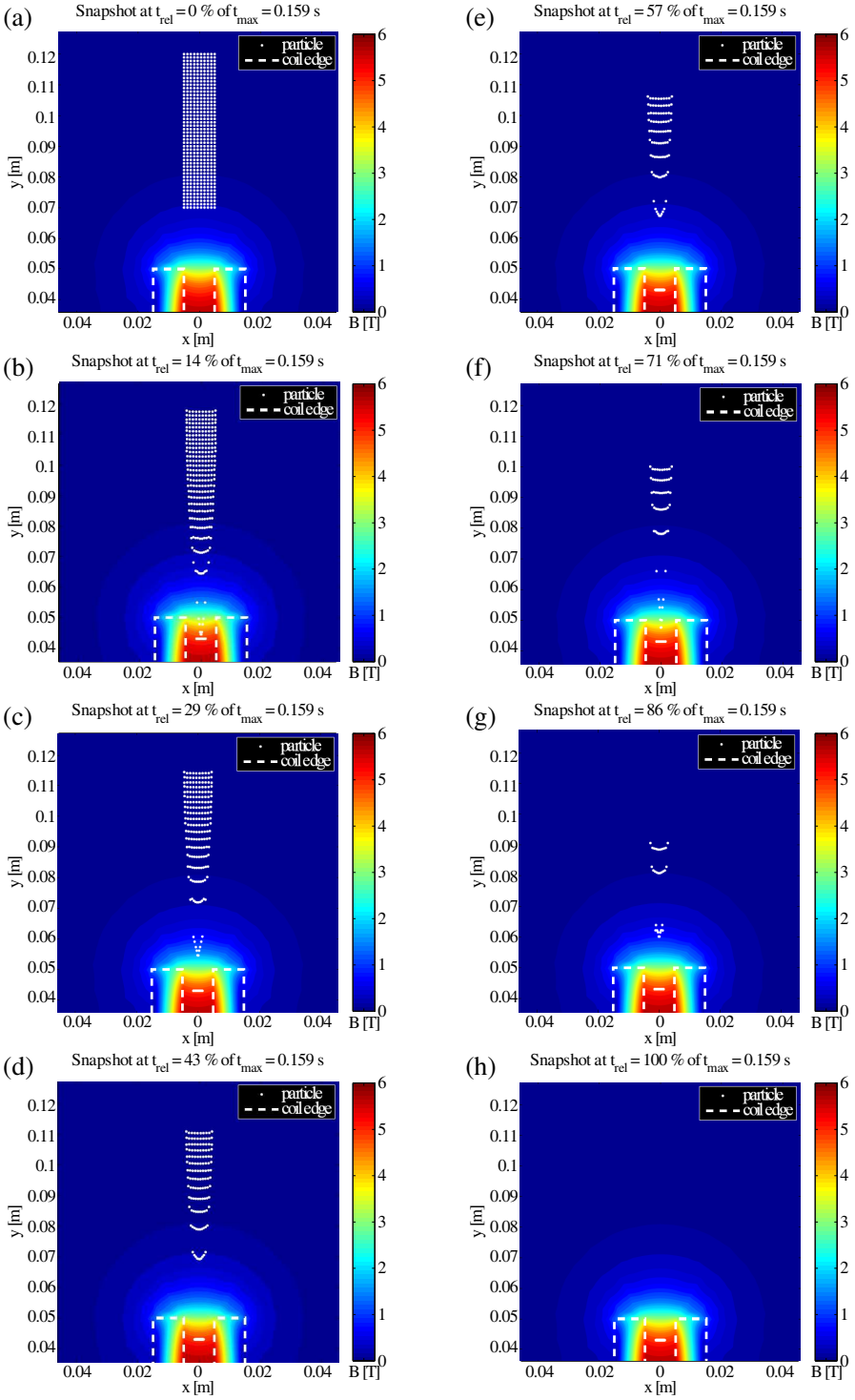

Figure 2. Snapshots of particles (magnetite spheres with diameter 10 µm) movement, with initial position equally spaced in the inlet of hand-hold coil in the generated magnetic field, in different times $t = (t_{rel}/100) \cdot t_{\max}$.

value 300 T/m in the case of hand-hold coil, exceeds gravitational force exerted on magnetite particles about 100–1000 fold, and has been therefore neglected, too. Furthermore, if we include gravitational force in our calculations with coils in vertical orientation, gravitational deposition will have an synergic effect on the acceleration of magnetic particles, though a little.

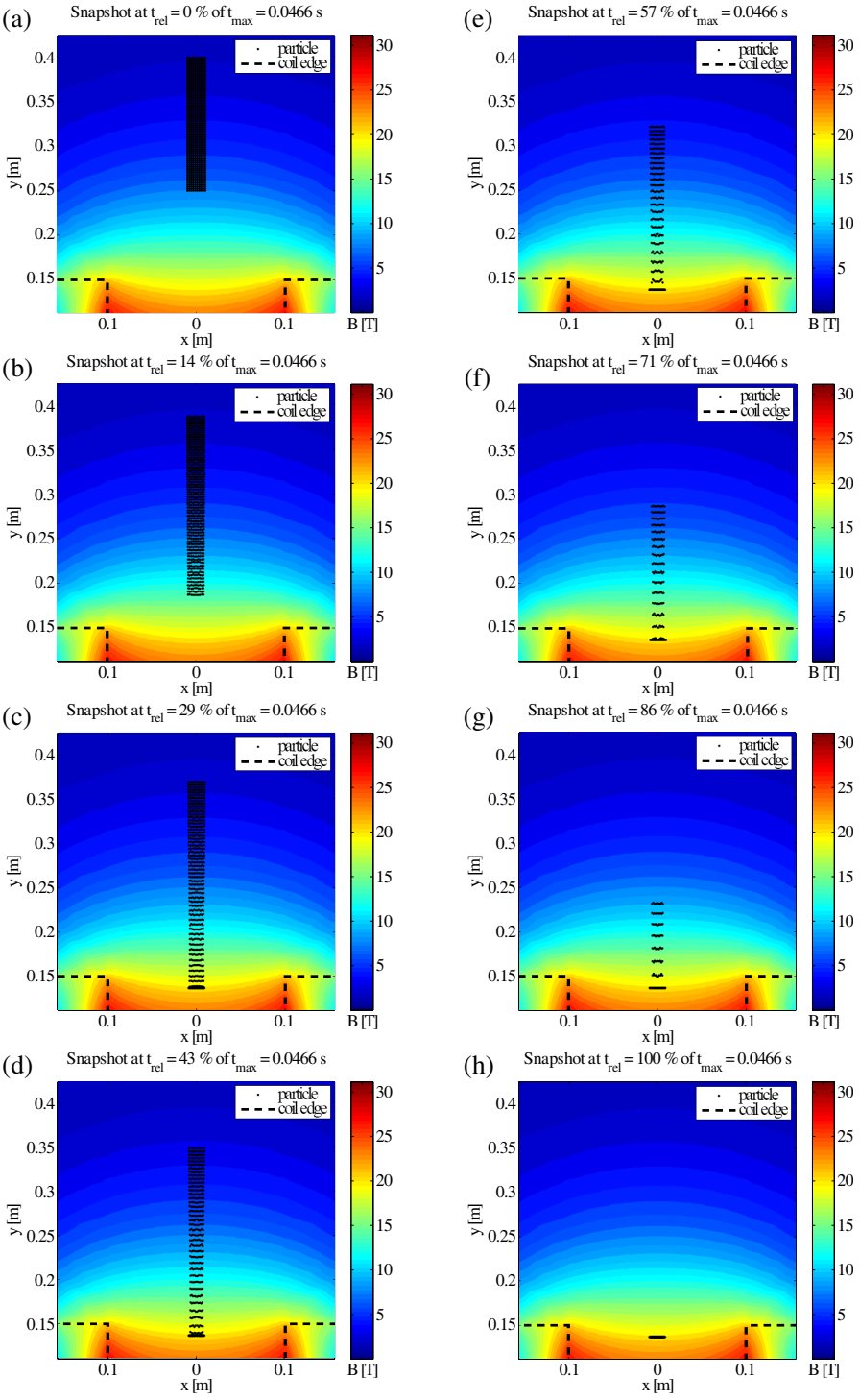

Figure 3. Snapshots of particles (magnetite spheres with diameter 10 μm) movement, with initial position equally spaced in the inlet of coil for infant lungs in the generated magnetic field, in different times $t = (t_{rel}/100) \cdot t_{\max}$.

We have simulated movement of the particles (used magnetite spheres with 10 μm in diameter) accelerated only with the gradient magnetic fields induced with two different coils: the small one — hand-hold coil, and the large one — the coil for infant lungs, as two cases. Particles have been slowed down with drag force of quiescent air ambient. They have been initially positioned with equally spaces

in the paraxial area of the coil's upper inlet, and magnetically pulled into the coil's opening where their movement have reached maximal velocity — optimal position for target location with maximal impact velocity. This velocity has reached values 21.6 and 17.8 m/s in the first (hand-hold coil) and the second (coil for infant lungs) case, respectively. The movement time of the last particle until its impact on the target location ($t_{\max}$) has been in these cases about 0.16 s (on the distance about 8 cm) and about 0.05 s (on the distance about 26 cm), respectively. Snapshots of particles' movement in the field of the hand-hold coil in different times specified as $t = (t_{rel}/100) \cdot t_{\max}$, as well as for the coil for infant lungs case are shown in respective on the Figs. 2 and 3.

Sanford et al. in their first high-pressure air jet experiment with simple air blast used tungsten spherical particles 4 μm in diameter to their successful incorporation into the onion epidermal cells by accelerating particles to incident velocity less than 400 m/s [33], what presents particle's momentum about 250×10^{-12} kg · m/s. In our computer aided simulations of magnetic acceleration of particles using magnetic ponderomotive force, magnetite particles with 10 μm in diameter have reached in both cases (of gradient magnetic field source: hand-hold coil and coil for infant lungs) relatively high maximal velocities, and in the case of hand-hold coil this value reached almost 22 m/s, what yields particle's momentum about 57×10^{-12} kg · m/s. That is almost comparable with Sanford's value, but it is important to point on larger cross-section of magnetite particles used by us in comparison with Sanford's ones what could have negative effect on success of intra-cellular gene delivery due to reduction of particle's impact pressure on target cell at the moment of impact. On the other hand, if our aim is to deliver gene into an animal or human cell culture instead of plant cells, there is no firm barrier like cell wall, what probably can reduce the particle's impact velocity (and momentum) value needed to overcome cell membrane and incorporation of particle into the cell.

Besides application of magnetic ponderomotive force for *in vitro* intra-cellular gene delivery, we proposed an idea of using same concept for *in vivo* acceleration of magnetic carriers to the lungs. As it is obvious from magnetic flux density (its gradient) plot on Fig. 1 or direction of particles' movement on Fig. 3, particles are primary directed to the coil cavity. By locating patient's airway (trachea) to the inlet of the coil and his chest to the location with maximal impact velocity of particles, it will be probably possible speed up particles enough for this issue. Presented simulations with quiescent air ambient would be equivalent to application of this technique in breath-holding situation. Also, magnetic fields of coils used in simulations are driven with DC for simplification as magnetostatic problem. Furthermore, by application of magnetically induced acceleration of particles in pulsing mode synchronized with breathing, during inhalation, it would be observed an synergic effect. For the generation of pulsed magnetic field can be used pulse magnetizer system which is a capacitor discharge type system that generates a few millisecond pulse of magnetic field with a peak value of 5–10 Tesla in the cylindrical fixture. Such a system are widely used for the preparation of permanent NdFeB magnets [43].

Although our results are based on a theoretical model which deserves experimental verification, using magnetic ponderomotive force instead of classical high pressure air jet gene may have many potential advantages like the reduction of side damage of targeted tissue due to the rapid air pressure change, which is in our approach completely avoided.

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