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Derivation of a Closed-Form Equation Describing the Magnetophoretic Velocity of Superparamagnetic Microbeads in Microfluidic Channels under the Influence of an External Magnetic Field

Paul Gomez[1], Ewa Wojcikiewicz[2] and Claudia Lopez[1]

[1]Quantum Nanoelectronics, Inc, Fort Lauderdale, Florida, USA
[2]Florida Atlantic University, College of Medicine, Boca Raton, Florida, USA

pgomez@qnanotronics.com

Abstract

The object of this research paper is to obtain an analytical function that describes the dynamics of motion of superparamagnetic beads in a microfluidic channel filled with a liquid such as water or blood under the influence of an external magnetic field. A closed-form equation was derived from first principles and then simulated using MATLAB® and the results compared to those obtained experimentally by other researchers.

This equation is an adequate tool to calculate the arrival times of functionalized magnetic beads of different radii at sensor location which might be useful in biomicrofluidics applications, specifically those that fall in the category of Lab-On-A-Chip in which segregation of bound and unbound beads could be determined on the basis of their different speeds without having to use magnetic separation and further external processing with additional instruments.

Additionally, a practical design equation was developed to calculate the operating point of a commercial electromagnet to obtain desired speeds at predetermined distances from the magnet's surface.

Keywords: *biotechnology, magnetophoretic, microbeads, microfluidic, Lab-On-A-Chip, superparamagnetic*

1. Introduction

In many microfluidic applications the use of functionalized superparamagnetic microbeads is widely used. Most of these microbeads consist of iron oxide (Fe2O3) superparamagnetic nanoparticles dispersed in a polymer matrix [1]. The microbeads are usually functionalized by covalently binding an antibody to the polymer matrix targeting specific biomolecules [2-4].

Since in most cases the object of funcionalized magnetic microbeads is to capture and immobilize target biomolecules in immunoassays, the dynamics of the mobility of the beads in the microfluidic channel is not quantified. However, the speed of beads bound to their target biomolecules is lower than the speed of beads that are not bound, that is, free of cargo. By comparing the different speeds and arrival times at an adequately placed sensor, a biochip would be able to recognize the presence of the molecule(s) of interest. For this reason we decided to study in more detail the displacement velocities of microbeads under the influence of externally applied magnetic fields.

Most researchers have arrived at a differential equation similar to Eq. (11) but instead of solving it have proposed to either, using numerical approximations such as FEA (Finite

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Element Analysis) [5], assuming that in a small range of interest the speed is constant and thus the acceleration is zero [6], using micromagnetic simulations with standard software such as ANSYS® or COMSOL® [7-10] or by simply measuring the speeds for their particular application [11].

Our contribution to the discipline of biomicrofluidics was to solve the differential equation (11) to obtain a closed-form equation that can be used to design a microfluidic biochip based on the speeds of the functionalized superparamagnetic microbeads.

2. Derivation of the Equation

Figure 1 shows the basic setting and restrictions of the model under study. It is assumed that the microbead is several orders of magnitude smaller than the magnet as is normally the case. It is also assumed that the magnet has a symmetrical shape such as square, rectangular or circular cross-section so that the only component of the magnetic field of interest lies in the direction of motion of the microbead. Also, it is assumed that the microbeads have diameters between 1 µm and 12 µm so that Brownian motion can be neglected [12]. Similarly, the gravitational force, mg, where m is the mass of the bead, is several orders of magnitude smaller than the magnetic pull force and thus can be neglected.

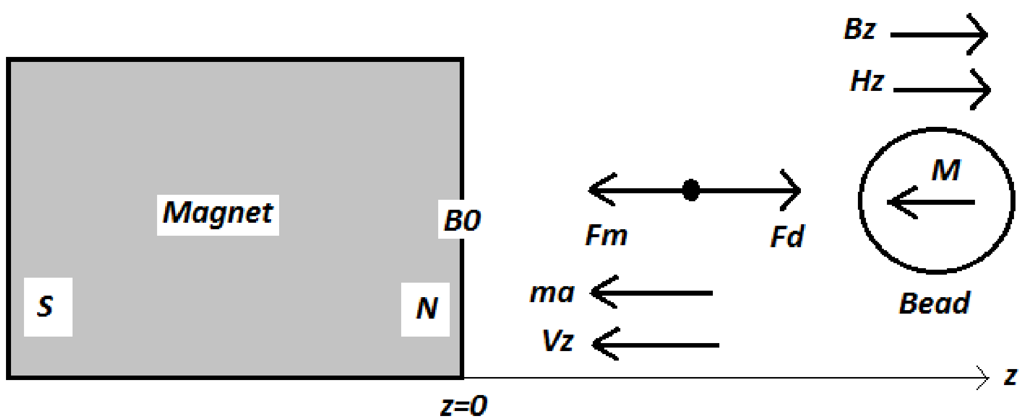

Figure 1. Basic setting

Since we are interested in the velocity in the axial direction of the magnet, Vz, and Vz is the only component of V, we will use velocity and speed interchangeably, although technically the first one is a vector quantity and the second is a scalar.

For the calculation of the magnetophoretic velocity of a superparamagnetic microbead moving under the influence of an externally applied magnetic field, we need to obtain the magnetic field and its gradient at every single point. The magnetic force exerted on a superparamagnetic bead of radius rb and magnetic susceptibility χ is [13]:

$$F_m = V_b J \frac{\partial H_z}{\partial z} \qquad (1)$$

Where J is the magnetic polarization

$$J = \mu_0 M \qquad (2)$$

M is the magnetization of the magnetic bead

$$M = \chi H_z \qquad (3)$$

below saturation [14], that is

$$M = \begin{cases} \chi H_z & |H_z| < H_c \\ M_s & |H_z| \geq H_c \end{cases} \qquad (4)$$

and V_b is the volume of the superparamagnetic bead which is assumed to have an almost spherical shape [1]

$$V_b = \frac{4\pi r_b^3}{3} \qquad (5)$$

Leading to:

$$F_m = V_b \mu_0 \chi H_z \frac{\partial H_z}{\partial z} \qquad (6)$$

A superparamagnetic bead of mass mb in a liquid such as water or blood subjected to an external magnetic field Hz is accelerated under the influence of two opposing forces, the magnetic force Fm and the drag force due to the viscosity of the fluid, Fd.

$$m_b \vec{a} = \vec{F}_m - \vec{F}_d \qquad (7)$$

Where the drag viscosity force, also known as Stoke’s drag is [14]:

$$\vec{F}_d = 6\pi\eta r_b \vec{v} \qquad (8)$$

The viscosity η is characteristic of each fluid. For water η=8.9x10-4 [Pa.s] and for blood varies between 2.8x10-4 and 3.8x10-4 [Pa.s]. It’s important to note that the force due to viscosity depends on the velocity and the size of the bead.

The mass of the magnetic bead is obtained with

$$m_b = \rho V_b \qquad (9)$$

Since $a = \frac{dv}{dt}$ we have (10)

$$m\frac{dv}{dt} = \mu_0 \chi V_b H_z \frac{\partial H_z}{\partial z} - 6\pi\eta r_b v \quad (11)$$

$$\frac{dv}{dt} = \frac{\mu_0 \chi V_b}{m} H_z \frac{\partial H_z}{\partial z} - \frac{6\pi\eta r_b}{m} v \quad (12)$$

By defining the following dummy variables:

$$k_1 = m \quad (13)$$

$$k_2 = \mu_0 \chi V_b H_z \frac{\partial H_z}{\partial z} \quad (14)$$

$$k_3 = 6\pi\eta r_b \quad (15)$$

We arrive at the following differential equation:

$$\frac{dv}{dt} = \frac{k_2}{k_1} - \frac{k_3}{k_1} v \quad (16)$$

Which has the general form:

$$\frac{dy}{dx} = f(x, y) \quad (17)$$

Or more generally

$$g(y)\frac{dy}{dx} = f(x) \quad (18)$$

with initial value $y(x_0) = y_0$

This differential equation has the general solution [15]:

$$\int_{y_0}^{y} g(y)dy = \int_{x_0}^{x} f(x)dx \quad (19)$$

In this particular case we have

$$dv = \left(\frac{k_2}{k_1} - \frac{k_3}{k_1} v \right) dt = \frac{1}{k_1} \left(k_2 - k_3 v \right) dt \tag{20}$$

Or

$$\frac{dv}{\left(k_2 - k_3 v \right)} = \frac{dt}{k_1} \tag{21}$$

with initial condition $v(0) = 0$

$$\int_0^v \frac{dv}{\left(k_2 - k_3 v \right)} = \int_0^t \frac{dt}{k_1} \tag{22}$$

The general solution for

$$\int \frac{dx}{ax + b} = \frac{1}{a} \ln(ax + b) \tag{23}$$

From which we have

$$- \frac{1}{k_3} \ln\left(k_2 - k_3 v \right) \Big|_0^v = \frac{t}{k_1} \Big|_0^t \tag{24}$$

$$- \frac{1}{k_3} \ln\left(k_2 - k_3 v \right) + \frac{1}{k_3} \ln\left(k_2 \right) = \frac{t}{k_1} \tag{25}$$

$$\ln\left(k_2 \right) - \ln\left(k_2 - k_3 v \right) = \frac{k_3 t}{k_1} \tag{26}$$

$$\ln\left(k_2 - k_3 v \right) = \ln\left(k_2 \right) - \frac{k_3 t}{k_1} \tag{27}$$

$$k_2 - k_3 v = e^{\ln(k_2)} e^{-\frac{k_3}{k_1} t} \tag{28}$$

$$k_2 - k_3 v = k_2 e^{-\frac{k_3}{k_1} t} \tag{29}$$

$$k_3 v = k_2 - k_2 e^{-\frac{k_3}{k_1} t} \tag{30}$$

$$v = \frac{k_2}{k_3}\left(1 - e^{-\frac{k_3}{k_1}t}\right) \tag{31}$$

And substituting the dummy variables k_1, k_2 and k_3 we obtain equation:

$$v_z = \frac{\mu_0 \chi V_b}{6\pi\eta r_b} H_z \frac{\partial H_z}{\partial z}\left[1 - e^{-\frac{6\pi\eta r_b}{m}t}\right] \tag{32}$$

Which is the velocity of the magnetic bead at distance z from the magnet.

From this equation it can be verified that the initial condition v=0 at t=0 holds. To verify this two-independent variable equation, we notice that the right term between parentheses is negligible due to the small mass of the bead which explains why gravitational force is not considered. Rewriting the velocity equation we arrive at the following simplified equation.

$$v_z = \frac{\mu_0 \chi V_b}{6\pi\eta r_b} H_z \frac{\partial H_z}{\partial z} \tag{33}$$

Using Eq. (5) to replace V_b in the above equation we arrive at our final equation:

$$v_z = \frac{2\mu_0 \chi r_b^2}{9\eta} H_z \frac{\partial H_z}{\partial z} \tag{34}$$

The values for H_z and its derivative can be found analytically for most magnets with symmetrical shapes as will be shown with an example in a following section. It can be seen from Eq. (34) that the speed is inversely proportional to the viscosity η as expected.

3. Verification with Experimental Results

To verify the validity of Eq. (34) we compare the results obtained by Hafeli *et al.*, [11]. They specifically designed an experiment aimed at measuring the velocities of several microbeads of different radii and magnetic susceptibilities at different magnetic fields and gradients.

The following table shows three of the microbeads used in the experiment for which all their parameters are known or could be calculated from the data. The last two columns are the calculated speed using Eq. (34) and the error percentage.

Table 1. Comparison of Experimental Results with Calculated Speed

Bead name	X (SI)	Diameter (μm)	η (Pa.s) (water)	H (A/m)	dH/dz	v (μm/s) Measured	v (μm/s) Calculated	Error (%)
Dynabeads® M280	0.3	2.8	9.33×10^{-4}	1.79×10^{4}	4.77×10^{6}	12.50±3.99	13.99	10.65
Specimen 1	0.03131	1.72	9.33×10^{-4}	1.03×10^{6}	1.11×10^{8}	48.9±30.2	69.78	29.93
Specimen 4	0.02665	1.74	9.33×10^{-4}	1.03×10^{6}	1.11×10^{8}	65.8±27.0	60.78	-8.25

The error was computed by comparing the calculated speed with the average measured speed. However, the measured speeds have a large variation and all the calculated speeds fall within the range of measured speeds, thus, the calculated speeds are adequate estimates of the expected speeds of the microbeads.

The susceptibility of Dynabeads® M280 at the experimental magnetic field and gradient was calculated from data from another study [17] by using the M.H curve (Figure 11 inset). For the Dynabeads® M280, 242 samples were measured and averaged; for Specimen 1 they used 110 samples and for Specimen 4, 149 samples were measured. A total of 501 samples with different susceptibilities and under different magnetic field strengths and gradients were measured and compared with our calculated speeds and found that when using Eq. (34) the calculated values are in agreement with the experimental results..

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4. Design Example Using a Commercial Electromagnet

As an example, we calculate the magnetic induction, magnetic field, field gradient and magnetophoretic velocity of Dynabeads® 450 moving under the magnetic field generated by a commercial electromagnet of cylindrical shape, part number EM050-6-222 from APW Company[18] with the following characteristics:

L = 0.5”, diameter (2a) = 0.5”, Fp = 2 lbs (pull force), $\mu r \approx 1900$ (Low carbon steel IASi 1800), Operates @6V and 0.16 A.

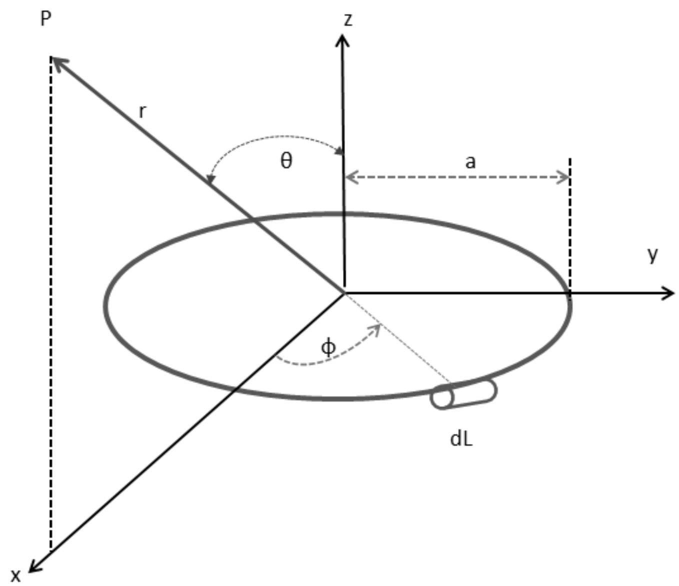

Figure 2. Magnetic field at point P due to a current loop

We begin by obtaining closed form equations for the magnetic induction, magnetic field and its gradient. The first step is to derive those variables for a circular current loop and then extend it to N loops which corresponds to the geometry of the electromagnet under study. The magnetic induction, B, on the radial direction at distance r from a circular current loop is defined by [19-20]:

$$B_r = \frac{\mu_0 I a^2 \cos\theta}{2\left(a^2 + r^2\right)^{3/2}}\left[1 + \frac{15 a^2 r^2 \sin^2\theta}{4\left(a^2 + r^2\right)^2} + \ldots\right]$$

We are interested in the value of B in the axial direction, that is, where θ=0. In the above equation the axial field reduces to:

$$B_z = \frac{\mu_0 I a^2}{2\left(a^2 + z^2\right)^{3/2}}$$

Where the variable r was substituted by z, the distance from the center of the loop to the point of interest in the axial direction. For a solenoid of radius *a*, length *L* and *N* turns and magnetic permeability μ we obtain:

$$B_z = \frac{\mu N I a^2}{2\left(a^2 + z^2\right)^{3/2}}$$

And

$$B_0 = \frac{\mu N I}{L}$$

at the center of the solenoid on the axis and approximately on the surface of the solenoid [51].

From which we obtain $NI = {B_0 L}/{\mu}$ and thus

$$B_z = \frac{\mu B_0 L a^2}{2\mu\left(a^2 + z^2\right)^{3/2}} = \frac{B_0 L a^2}{2\left(a^2 + z^2\right)^{3/2}}$$

$$B = \mu H$$

And outside matter [20]

$$H_z = \frac{B_z}{\mu_0} = \frac{B_0 L a^2}{2\mu_0\left(a^2 + z^2\right)^{3/2}} = \frac{B_0 L a^2}{2\mu_0}\left(a^2 + z^2\right)^{-3/2}$$

And the gradient in the axial direction:

$$\frac{\partial H_z}{\partial z} = \frac{B_0 L a^2}{2\mu_0}\left(-\frac{3}{2}\right)\left(a^2 + z^2\right)^{-5/2}(2z)$$

$$\frac{\partial H_z}{\partial z} = \frac{-3 B_0 L a^2}{2\mu_0} z\left(a^2 + z^2\right)^{-5/2}$$

The above equation is more practical because manufacturers of off-the-shelf electromagnets usually provide the geometry and the pull-force of the magnet. From the pull force we can find B_0 as follows.

Given an electromagnet of radius a, length L and pull force Fp in pounds the following formulas are used:

$F_N = 4.45 F_p$ To convert from pounds to Newtons.

$$F_N = \frac{B^2 \pi a^2}{2\mu_0}$$

$$B^2 = \frac{2\mu_0 F_N}{\pi a^2}$$

$$B_0 = \frac{1}{a}\sqrt{\frac{2\mu_0 F_N}{\pi}}$$

Using the above equation we obtain an approximate value for B_0.

$B_0 \approx 0.42$ T

Using this equation with the electromagnet given as an example above, for which B0 ≈ 0.42 T with a Dynabead with diameter of 4.5 μm and susceptibility and χ=1.63 moving in blood with average viscosity η=3.3x10-4 we obtain the fields and velocity shown in the following figures.

For a Dynabead superparamagnetic bead of diameter 4.5 μm [6] it was found that ρ=1600 Kg/m3.

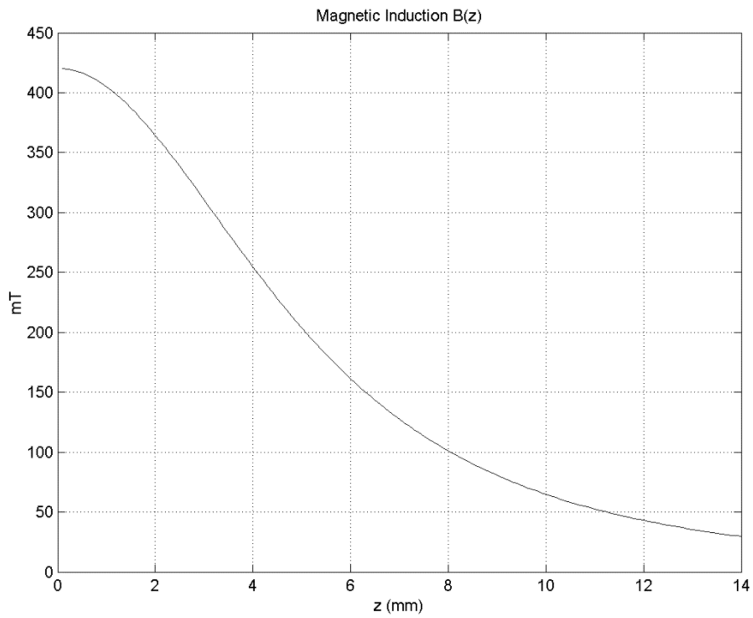

Figure 3. Magnetic Induction B(z)

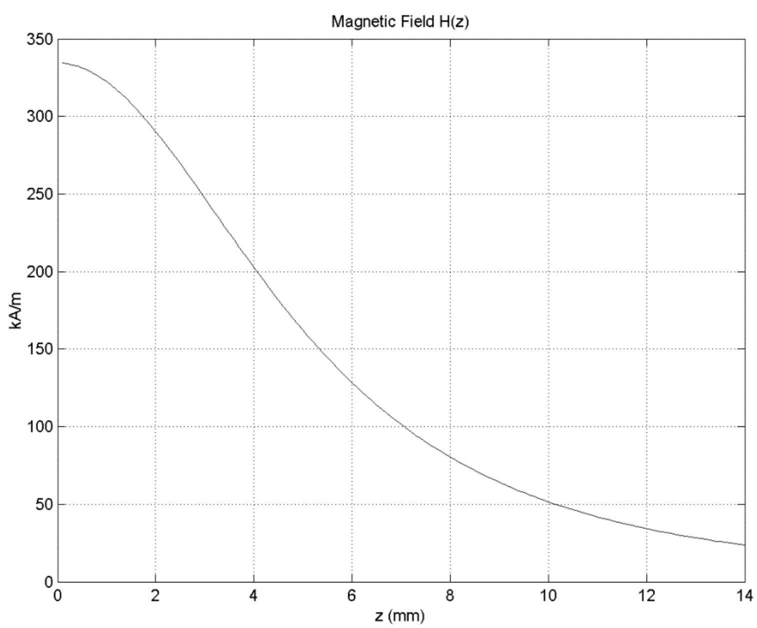

Figure 4. Magnetic Field H(z)

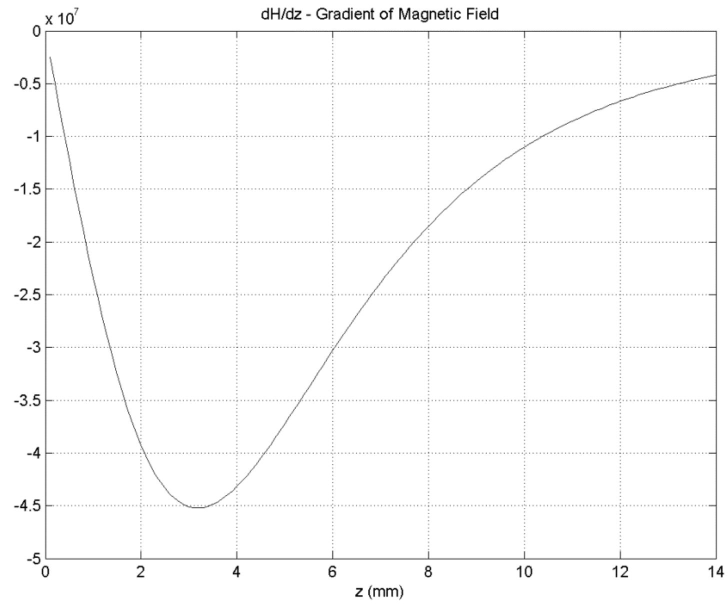

Figure 5. Magnetic Field Gradient dH/dz(z)

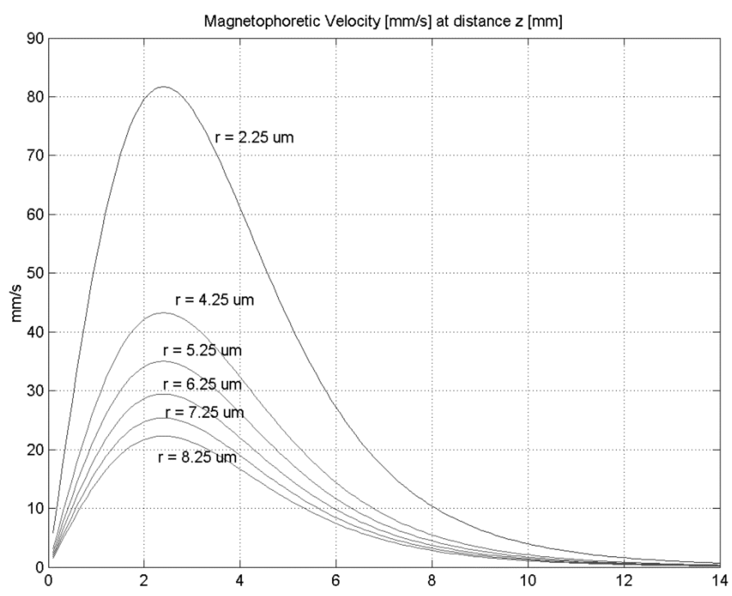

Figure 6. Speed of magnetic beads of several radii

From the curves it can be seen that the sensor should be located around 3 mm from the magnet's surface where the differences in speed are larger.

5. Conclusions

A closed-form equation describing the magnetophoretic velocity superparamagnetic microbeads subjected to external magnetic fields was obtained from first principles and verified with experimental results. The calculated speeds were in good agreement with the measured speeds and thus this equation can be used to model and design biochips that make use of functionalized magnetic microbeads. Our future work will be to use this equation and the simulations developed on this research to design a microchip capable of sensing the presence of metastatic cancer cells in the circulation.

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Authors

Paul Gomez, PhD. Dr. Gomez is the Chief Scientist at Quantum Nanoelectronics, Inc. a company based in South Florida, USA. Dr. Gomez holds BSEE, MSEE an PhD in Electrical Engineering from Florida International University, Miami, USA. He has more than 25 years of experience as engineer, researcher and educator.

Ewa Wojcikiewicz, PhD. Dr. Wojcikiewicz is an Assistant Professor of Biomedical Science at the Faculty of Medicine at Florida Atlantic University, Boca Raton, Florida, USA. She holds a PhD in Biophysics from the University of Miami.

Claudia Lopez. Miss Lopez is a Research Engineer at Quantum Nanoelectronics, Inc. a company based in South Florida, USA. She holds an Engineering Degree and Master of Business Administration MBA, from Nova Southeastern University, Davie, FL, USA. She has more than 20 years of experience as a professional engineer.