Physics-Based Nanomedicine to Alleviate Anomalous Events in the Human Kidney

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Abstract. Commonly the type-2 diabetes complications are imminent in those organs where is a substantial dependence of the microvascularity such as for instance the renal apparatus that it might be substantially affected. One of the points related to this is the degradation of the kidney functions fact that is accompanied without any symptomatology or some signals that allow the identification of the beginning of the so-called diabetes kidney disease. It is noteworthy that for large periods, clinicians have reported that type-2 diabetes patients might be potential candidates to use the dialysis machines. Therefore, to attack the problem of how to tackle down the beginning of the renal disease in type-2 diabetes would require to understand the phenomenon that is carried out in the kidney, particularly in the renal glomerulus, or glomerulus in short. In this paper we take advantage of the physics-based phenomenology to develop closed-form expressions that would describe the different scenarios by which the glomerulus is invaded by giant proteins like the albumin. Under this scenario, albumin proteins that are pushed out by the glucose dipoles in blood are expected to exert repulsion as well as attraction forces inside the glomerulus. Thus, there is a large probability as to expect that the departure of the bunches of albumin from sensitive microvascularity inside the kidneys can reach the Bowman's space and the urine formation zone. In this paper we present a study of the physics interactions inside the renal glomerulus. Essentially we use physics equations to derive the laws that govern the pass of proteins such as albumin through the layers of glomerulus. Once the physics equations are established the albumin excretion ratio is estimated. Basically, proteins do interact with glomerulus through the remaining charges along the layers and podocytes. This is crucial to determine the volume of albumin that goes to the Bowmam's space. Our study uses physics equations inside of the framework of charge electric density. The fact of measure accurately the quantity of excreted albumin with physics equations, provides capabilities to apply precise strategies in the side of the clinicians to improve the treatment in the cases where there is a potential risk to acquire the well-known diabetes kidney disease. All these methodologies encompass with the prospective Internet of Bio-Nano Things that engages an Internet network with human organs in order to anticipate any eventual abnormality or wrong functionality of organs in real-time.

Keywords: Renal damage · Kidney · Nephropathy

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1 Introduction

One of the main and critical complications of type-2 diabetes [1] is the so-called diabetic nephropathy by which the kidneys exhibit a degradation in their functionalities [2], fact that is manifested in the anomalous excretion of proteins. In normal scenarios, albumin and Tamm Horsfall proteins are excreted through the urine. In humans, the Tamm Horsfall protein turns out to be abundant surpassing in volume to the albumin that should be excreted to a minor extent.
In people that have had a diagnostics of type-diabetes, the concentrations of glucose in blood might not to follow a linear behavior as to the intake of carbohydrates and sugars, since the mean values of glucose might jump above the allowed ones. Therefore, during the periods where the patient exhibits large concentrations of glucose in blood, in some organs that are composed by micro microvascularity or micro veins, there is a potential risk that these organs manifest abnormalities and therefore it is established the beginning of a certain disease that would have implications in the instability of homeostasis. Due to the electric constitution, the dipoles of glucose might cancel the shield of negative charges located in the different layers of glomerulus whose task is to stop the pass of charged electrically proteins. Thus, the abundance of dipoles becomes proportional to the amount of negative charges along the layers. Once the layers are unprotected, albumin proteins pass through the urine formation zone [3]. It is sketched in Fig. 1. The rest of this paper is structured as follows: in second section we described briefly the concept of Nanomedicine used in this paper. Third section describes the physics model and the formalism to estimate the electric forces is described as well as the basis for an efficient detection of albumin proteins. Fourth section is devoted to the calculation of the repulsion force that is expected between the albumin bunching and the nano sensor. In fifth section the AER is estimated and the attained uncertainty is estimated. Finally, the conclusion of the paper is drawn.

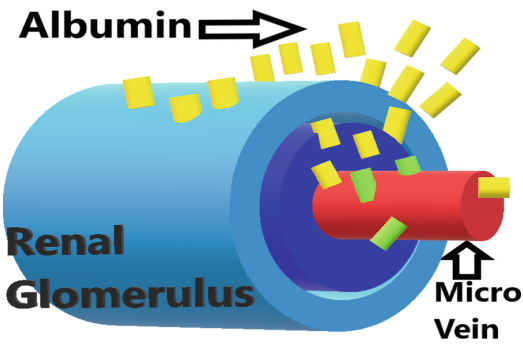

Fig. 1. Sketch of the assumed electrodynamics in the renal glomerulus: abundance of glucose might be the first cause for releasing of albumin proteins that travel through the layers of glomerulus escaping to the urine formation zone.

2 The Concept of Nanomedicine in This Paper

Since the beginning of the DKD might not have any symptomatology, classic medicine requires of test and at least a minimum window to suggest a certain pharmacology when the clinician has probed that the patient has already manifested some first symptoms that would correspond to the last phases of disease [4]. In this stage the patient might not have a back way because DKD is irreversible and a possible alteration of others organs might be observed. Certainly, the time between a first manifestation of DKD and the last phase is thought to be a decade. Therefore the idea to use the so-called Nanomedicine as an advanced methodology to alleviate and improve the renal functionality appears as an robust alternative due to:

- the emergence of nanotechnology [5],
- the apparition of prospective and advanced Internet networks [6],
- the arrival of computational systems based driven by big data,
- the wide understanding of the very beginning of DKD through physics concepts.

Figure 1 exhibits the main point of this paper: the dynamics of charges compounds in the renal glomerulus. Gian Marco Ghiggeri was the first whom observed electrical properties in human albumin [7]. This certainly opens various windows of studies in the territory entirely governed by physics laws.

Therefore the anticipation of this dynamics is inside of the territory of physics in the sense that because exists a well-defined scenario whose rules are established by physics equations, then the implementation of advanced devices that sense and perform charge measurements inside the glomerulus renal, then it might be seen as a novel methodology to estimate the level of degradation of the kidneys for instance, as well as a tool to make precise interventions against the presence of charge compounds. When these advanced devices are the so-called nanorobots, then the scenario by which the kidney is treated against next potential phases of degradation and dysfunction.

3 Physics Models of Invasion of Albumin Proteins in the Renal Glomerulus

3.1 The Diffusion Equation

The diffusion of albumin proteins through the layers, can be done through the well-known diffusion equation

$$\frac{\partial}{\partial t}u(\mathbf{r},t) = D\boldsymbol{\nabla}^2 u(\mathbf{r},t), \tag{1}$$

where D the diffusion's constant. As seen in Fig. 1, an acceptable coordinate system to apply Eq. (1) becomes the cylindrical system by which one can anticipate

that the albumin would exhibit radial trajectories. Under this reference system, then we can write down:

$$\frac{1}{D}\frac{\partial}{\partial t}u(\mathbf{r},t)=\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}u(\mathbf{r},t)\right)+\left(\frac{1}{r^2}\frac{\partial^2}{\partial\theta^2}+\frac{\partial^2}{\partial z^2}\right)u(\mathbf{r},t). \tag{2}$$

The usage of the method of separation of variables lead us to write the function $u(\mathbf{r},t)=R(r)\Theta(\theta)Z(z)T(t)$, so that we can obtain

$$\frac{1}{DT(t)}\frac{dT(t)}{dt}=-\lambda \tag{3}$$

$$\frac{1}{rR(r)}\frac{\partial}{\partial r}\left(r\frac{\partial R}{\partial r}\right)+\left(\frac{1}{\Theta r^2}\frac{\partial^2\Theta}{\partial\theta^2}+\frac{1}{Z}\frac{\partial^2 Z}{\partial z^2}\right)=-\lambda. \tag{4}$$

Eq. (2) is solved in a straightforward manner resulting in $T(t)=T_0\mathrm{Exp}(-\lambda Dt)$. However, Eq. (3) implies that $\frac{1}{Z}\frac{\partial^2 Z}{\partial z^2}=-m^2$ so that $\frac{1}{rR(r)}\frac{\partial}{\partial r}\left(r\frac{\partial R}{\partial r}\right)+\frac{1}{\Theta r^2}\frac{\partial^2\Theta}{\partial\theta^2}+k^2$ and $\frac{1}{\Theta}\frac{\partial^2\Theta}{\partial\theta^2}=-\ell^2$ with ℓ an integer number, and finally we have

$$\phi^2\frac{d^2R}{d\phi^2}+\phi\frac{dR}{d\phi}+\left[\phi^2-\ell^2\right]R(r)=0, \tag{5}$$

with $\phi=qr$, and $q=\sqrt{\lambda-m^2}$ and which is essentially the Bessel's equation with general solution: $R(\phi)=\mathcal{A}J_\ell(\phi)+\mathcal{B}J_{\ell+1}(\phi)$. On the other hand, $\Theta(\theta)=\mathcal{C}_\ell\mathrm{Sin}(\ell\theta)+\mathcal{D}_\ell\mathrm{Cos}(\ell\theta)$ and $Z(z)=\mathcal{A}_m\mathrm{Sin}(mz)+\mathcal{B}_m\mathrm{Cos}(mz)$. With the boundary conditions, $m=\frac{n_1\pi}{z_1}$ and $\ell=\frac{n_2\pi}{\theta_1}$, with $n_{1,2}$ integer numbers, and z_1 and θ_1 values corresponding to the geometry of glomerulus and $q\approx\sqrt{\lambda}$,

Boundary Conditions. According to Fig. 1 we have imposed two well-defined boundary conditions for the radial part:

- $R(qr_1)=0$ for $t_0=0$ that means that the flux of albumin proteins starts from this radius $r=r_1$, whereas for $r=r_2$ exists a substantial flux of bunches of albumin and other types of proteins that are crossing the glomerulus [8] whose length might be given by the distance $r_2-r_1\approx 100$ nm.
- And $R(qr_2)=\mathcal{R}$ that denotes that the concentration of proteins just in $r=r_2$ has a determined values namely $\mathcal{R}$ for $t>t_0$. For this time the bunches of proteins have evolved in time. The fact of imposing a solution with the index $\ell+1$ is due to that these boundary conditions a solution of the form $AJ_\ell+BJ_{\ell+1}$ is not admitted, because it results in a trivial solution.

Thus one would expect that a nano sensor is located near to the region of proteins evacuation to guarantee that negatively charged proteins might be enough efficient to discriminate them from the noise. By knowing the size of the

albumin protein of order of 10 nm a possible size of the nano sensor would be of order of 100 nm. In this manner a closed-form solution of (1) is written as

$$\rho_{\rm A}(\mathbf{r},t)=\rho_0{\rm Exp}^{[-\lambda D(t-t_0)]}\times$$
$$\times\sum_{\ell=-\infty}^{\infty}\frac{{\rm Sin}\left(\frac{n_1\pi z}{z_1}\right){\rm Sin}\left(\frac{n_2\pi\theta}{\theta_1}\right)\left[J_{\ell+1}(qr_1)J_\ell(qr)-J_{\ell+1}(qr)J_\ell(qr_1)\right]}{J_\ell(qr_2)J_{\ell+1}(qr_1)-J_\ell(qr_1)J_{\ell+1}(qr_2)}, \tag{6}$$

Thus the total charge derived from this solution is $Q_{\rm A}=\int\rho_{\rm A}(\mathbf{r},t)dV$.

3.2 The Jackson Equation

Again, as seen in Fig. 1, the assumption that the glomerulus follows a cylindrical geometry makes us to test a different approach entirely based on classical electrodynamics. In contrast to the previous approach classical electrodynamics [9] does not contain the time so that all solutions are fully independent of time. **This view fits in a convenient manner the modeling of a charged nano sensor deployed inside the layers of kidney being one of them the renal glomerulus**.

Therefore the nano sensor is modeled through a charge $\mathcal{Q}$ inside of a volume belonging to the renal glomerulus. Thus this charge produces a electric potential to a distance measured by the vector $\boldsymbol{R}=\mathbf{r}-\mathbf{r}'$, where the full charge $\mathcal{Q}$ is located in $\mathbf{r}$ and the potential is calculated in $\mathbf{r}'$. The solution to this problem turns to be as the so-called Jackson potential. The potential is given in [11], $\Phi(\mathbf{r},\mathbf{r}')$ depends is the cylindric parameters L and a and the full charge containing inside $\mathcal{Q}$. Because the charge $\mathcal{Q}$ is fixed there is not time dependence as argued claimed above. According to the Poisson's equation the associated charge density satisfies the differential equation given by:

$$\nabla^2\Phi(\mathbf{r},\mathbf{r}')=-\frac{\rho(\mathbf{r},\mathbf{r}')}{\epsilon}, \tag{7}$$

The full closed-form solution is expressed as:

$$\rho_B(\mathbf{r},\mathbf{r}')=-\epsilon\nabla^2\Phi(\mathbf{r},\mathbf{r}')=$$
$$-\frac{2\mathcal{Q}}{\pi La^2}\sum_{\ell,m,n}\frac{{\rm Exp}[im(\theta-\theta')]{\rm Sin}\left(\frac{\ell\pi z}{L}\right){\rm Sin}\left(\frac{\ell\pi z'}{L}\right)}{\left[\left(\frac{\xi_{m,n}}{a}\right)^2+\left(\frac{\ell\pi}{L}\right)^2\right]J^2_{m+1}(\xi_{m,n})}\frac{\ell\pi}{4L}J_{m+1}(\frac{\xi_{m,n}r'}{a})\times \tag{8}$$
$$\frac{\xi_{m,n}}{4a^2}[\xi_{m,n}J_{-2+m}(\frac{\xi_{m,n}r}{a})-J_m(\frac{\xi_{m,n}r'}{a})-\xi_{m,n}J_m(\frac{\xi_{m,n}r'}{a})-J_{2+m}(\frac{\xi_{m,n}r}{a})],$$

with a sign negative, therefore the total charge can be written as

$$\mathcal{Q}=-\int\epsilon\nabla^2\Phi(\mathbf{r},\mathbf{r}')d^3\mathbf{r}' \tag{9}$$

where $\mathcal{Q}$ that is located in r',θ',z' denotes the charge of the nano device that is the source of electric field in the point r,θ,z.

4 Closed-Form Expressions of the Electric Charges and Force

With Eqs. 6 and 9 the charges that under interaction will produce a electric force, the full electric force created by the repulsion of the nano sensor and the negative charged bunches of albumin is obtained in a straightforward manner from

$$\mathcal{F} = \int \frac{\mathcal{Q}\mathcal{Q}_{\mathrm{A}} d^3\mathbf{r}'}{|\mathbf{r}-\mathbf{r}'|} \tag{10}$$

with the previous equations the full electric force that would involve the nano sensor and the bunching of albumin reads

$$|\mathcal{F}| = \frac{1}{4\pi\epsilon}\int \frac{\int \epsilon\nabla^2\Phi(\mathbf{r},\mathbf{r}')d^3\mathbf{r}' \int \rho(\mathbf{r},t)d^3\mathbf{r}}{|\mathbf{r}-\mathbf{r}'|^2} \tag{11}$$

that is actually the strength of the electric force in the radial direction in the sense that the albumin escapes along the radial direction under the assumption that the glomerulus has the cylindrical shape. Due to the fact that the bunches of albumin are charged electrically compounds, then is of interest to calculate the full electric charge that might be sensed by a nano sensor.

Fixed Volume of Nano Sensor

In order to extract a value of this electric force, we assume that the charge of nano sensor follows $\mathcal{Q} = \rho\Delta V = \rho\Delta z R\Delta R\Delta\theta$ thus in this manner we have

$$|\mathcal{F}_R| = \frac{1}{4\pi}\int \frac{\int \rho(\mathbf{r},t)d^3\mathbf{r}\rho\Delta z R\Delta R\Delta\theta}{|\mathbf{R}|^2} \tag{12}$$

while the nano device dimension left fixed $\Delta z R\Delta R\Delta\theta$ = constant then the volume is compact,

$$|\mathcal{F}_R| = \frac{1}{4\pi}\int \frac{\int \rho(\mathbf{r},t)d^3\mathbf{r}\mathcal{Q}_N}{|\mathbf{R}|^2} \tag{13}$$

$$|\mathcal{F}_R| = \frac{1}{4\pi}\int J_{\ell+1}(qr_1)J_\ell(qr)\frac{\mathcal{Q}_N}{r^2}dV = \frac{1}{4\pi}\mathcal{Q}_N\int^r \frac{J_{\ell+1}(qr_1)J_\ell(qr)}{r^2}dV$$

by taking into account the factor 2 in Eq. 8 we can arrive to:

$$|\mathcal{F}_R| = \frac{1}{4\pi}2\mathcal{Q}_N d\theta dz\int^r \frac{J_{\ell+1}(qr_1)J_\ell(qr)}{r^2}dr \tag{14}$$

with the integration over the product of two integer-order Bessel functions that can be done in a closed-form yielding:

$$|\mathcal{F}_R| = 2\mathcal{Q}_N\Delta\theta\Delta z\left[\frac{J_n(r)J_m(r)}{r(m+n+1)} + \frac{J_{n-1}(r)J_m(r)+J_n(r)J_{m-1}}{(m+n)^2-1}\right] \tag{15}$$

In Fig. 2 are shown the electric forces calculated with Eq. (15). The fact of the assumption that the nano sensor has a well-defined volume and charge

the calculation as seen in (15) has shown to be exact. In Fig. 2 the different manifestations of the electric force have been plotted. For example in Top panel the force is plotted but only the first term of numerator is taken. The cases (a) to (e) denote the orders m and n. The peaks here are understood as all those distances by which the flux of albumin is maximum. The position of these peaks follows the used orders in the Bessel functions. In middle plot the normalized force taking into account both terms of numerator is plotted. For example the case (A) displays a morphology that can be understood in terms of the sign of the charge distributions. A first peak is seen in 0.20 μm and subsequently a minor peak is seen in 1.23 μm. Although this minor peak might be explained in terms of the decreasing of flux of albumin [10], also it can be interpreted as the flipping of the sign of the nano sensor. The usage of high orders of the Bessel functions displays similar shapes as (A). The cases (B), (C), and (D) emerge as the fact that in large distance from the micro microvascularity the intensity falls down since the possible apparition of positive charges would cancel a substantial part of the bunches of albumin so that the force intensity becomes small. The black arrows point the peaks by which one expects that the flux is substantial as for limiting the strength of the electric force. In bottom panel the formation of successive peaks is seen. Here we consider the whole expression Eq. 15. Interestingly the curve (B) for the distances between 1.5 μm and 3.0 μm the electric force turned out to be negative with the minor peaks in (B) and (C) still with positive values. In large distances, curve (A) recover the initial sign and becomes positive. Clearly this behavior is responding to one of character entirely oscillatory more than a linear dynamics as assumed previously. In virtue to this we can establish the following:

- Oscillations of the sign of the electric force might have as origin the unbalancing of the charge distributions along the renal glomerulus,
- The nano sensor has as function to change its sign through external bio cyber interfaces,
- The pass of large bunches of albumin might to trigger nonlinear dynamics in the electrical interactions.

4.1 The Full Electric Force

A special scenario constitutes the one where the electric force is dependent on the time. To include the time in the full formulation of the strength of the electric force we shall use the solution of the diffusion equation that involve the exponential dependent on the time. Considering the existence of attraction and repulsion forces, then we can write down

$$\boldsymbol{F}_R(\boldsymbol{r},t) = \frac{2\mathcal{Q}_N\rho_0 \mathrm{Exp}(-\lambda D t)}{\pi\epsilon L a^2}\sum_{\ell,m,n}\int 4\pi r^2 dr J_{-2+m}(\frac{\xi_{m,n}r}{a})J_{\ell-1}(qr), \quad (16)$$

$$\boldsymbol{F}_A(\boldsymbol{r},t) = -\frac{2\mathcal{Q}_N\rho_0 \mathrm{Exp}(-\lambda D t)}{\pi\epsilon L a^2}\sum_{\ell,m,n}\int 4\pi r^2 dr J_{2+m}(\frac{\xi_{m,n}r}{a})J_{\ell+1}(qr), \quad (17)$$

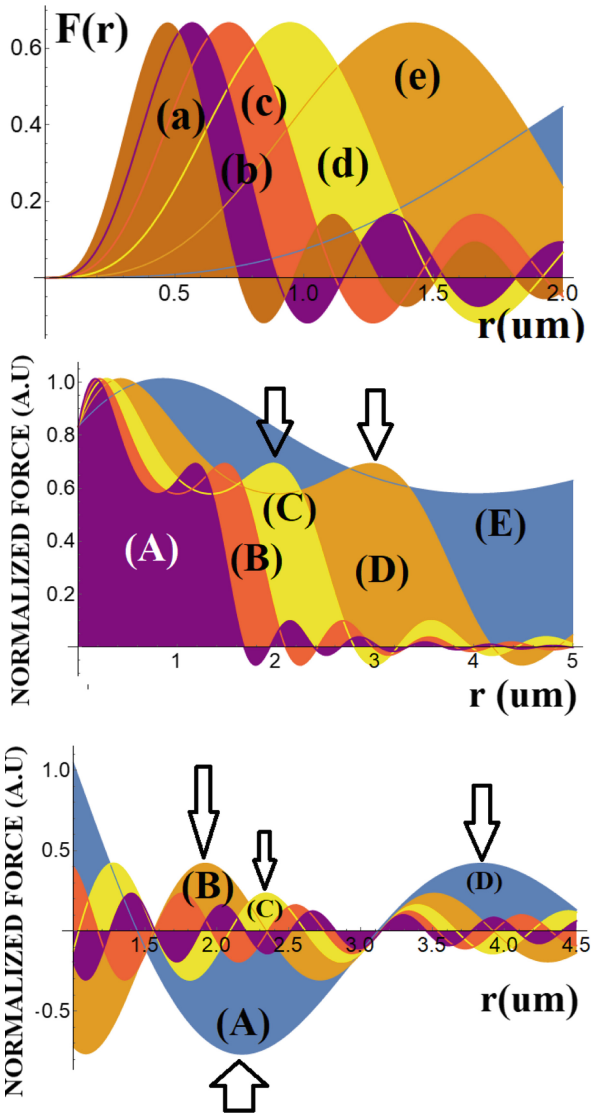

Fig. 2. Top: The electric force (expressed in arbitrary units versus the radial distance measured in μm. Middle and bottom: the normalized electric force as function of the radial distance expressed in μm. The order of the curves follows the order of the Bessel function from the lower until the higher order. In these simulations, (A)–(E) run between from the 0-order to the 7-th order.

by which is imminent that $\boldsymbol{F}_R(\boldsymbol{r},t) + \boldsymbol{F}_A(\boldsymbol{r},t) = 0$.

To investigate in certain details the attraction forces inside the renal glomerulus we consider the rate of full radial component electric force is written as:

$$\frac{\Delta \boldsymbol{F}_A(r,t)}{\Delta r} = -\frac{R^2 \mathrm{Exp}(-\lambda D t)}{(1-\gamma)^2} \sum_{\ell,m,n} \frac{J_{2+m}(\frac{\xi_{m,n} r}{a}) J_{\ell+1}(qr)}{r^2}. \tag{18}$$

Equation (18) is relate out with the energy that would expend the nano device once that it acquires mechanical motion. The quantity R denotes the radius of the spherical space by which the nano sensor is expected to be moving inside. Thus this energy is defined as

$$\mathcal{E} = \frac{||\Delta \boldsymbol{F}_A(r,t)||}{\Delta r}\mathcal{A} \tag{19}$$

where $\mathcal{A}$ the effective area that the nano device passes on it. In terms of prospective and realistic usage is expected that the nano device should move inside the smallest portions of area in the kidney in order to avoid damage by physical contacts between the device and tissues.

Since we are dealing with classical physics, the entire energy due to electric interactions between the nano device and the bunch of proteins is perceived as one of harmonic origin in the sense that the energy is driven by $\mathcal{E} = m\omega^2 x^2/2 + m_N v^2/2$ where m_D the nanodevice mass. For small velocities the pure kinetic term is neglected, in this manner the period of oscillation of the nanodevice appears to be as:

$$T = \pi r \sqrt{\frac{2 m_N \Delta r}{||\Delta \boldsymbol{F}(r,t)||\mathcal{A}}} \approx \pi r \sqrt{\frac{2 m_N}{\mathcal{E}}}. \tag{20}$$

The Physical Action

Starting from the fact that the action becomes the product of energy by time then with (19) and (20) we have

$$\mathcal{S} = \pi r \sqrt{\mathcal{A}||\Delta \boldsymbol{F}(r,t)||2 m_N \Delta r} \tag{21}$$

that implies that the action is proportional to the root square of the mass of the nano sensor, denoting the importance of the physics properties of the nano sensor to adjust electric dynamics in the renal glomerulus. This fact is seen also from the angle of the powering engineering that targets to provide energy to the nano sensor in order to extend the most large lifetimes when is working in the renal glomerulus.

In order to numerically evaluate Eq. 18 we have plotted in Fig. 3 distributions of dF/dr (assuming SI units) for the cases of repulsion (same sign) and attraction (opposite signs) between the bunch of albumin and the nano sensor. We can see that in both cases that the forces fall down as the increasing of the order of the Bessel function as seen in Fig. 2.

Certainly the large peaks is done for the first orders. Roughly speaking the flipping of the sign in the force is driven by the net amount of positively charged proteins. Physically speaking this makes that the proteins are attracted to the proximity of the nano sensor. Contrarily, the case where the bunch and nano sensor are same sign the **repulsion can be seen a mechanism that expels and detains the exit of successive trains of bunches of albumin through the Bowman's space**.

In Table 1 are listed the input values that yields a crude estimate of the period of oscillation of the nano sensor. Thus under the assumption that 1 pulse electromagnetic is emitted by the nano sensor per an entire period of 0.04 s under the event of attraction or repulsion then a total of 90,000 pulses per hour are expected to be sent by the nano sensor to the bio cyber interface inside the framework of the Internet of Bio-Nano Things. Clearly the expected bio cyber device is expected to be able to discriminate the true signal *i.e* the albumin proteins against noise or background such as the Tamm-Horsfall proteins. Therefore this prospective nano sensor is expected that might learn from the experienced oscillations to recognize albumin proteins from others proteins that would not turn out to be hostile chemical compounds against the glomerular zone as well as the intrinsic functionalities of kidney [11].

Table 1. Numerical Estimates of Eq. 20.

Quantity	Value	Error
$\mathcal{E}$	10^{-10} Nm	$\pm 1\%$
m_N	10^{-6} Kg	$\pm 0.5\%$
r	10^{-4} m	$\pm 0.05\%$
T	4.42 10^{-2} s	± 0.75 %

5 Estimation of the Albumin Excretion Rate

5.1 Theoretical Derivation

Normally, the AER parameter used extensively in the diagnosis of the early renal disease is expressed in terms of mg/dL as well as mg/24 h. Advanced phases of the so-called albuminuria can reach or surpass 300 mg/24 h. Thus, from Eq. 20 the energetic observable is related to the kinetic energy of the bunching of albumin leaving the renal glomerulus,

$$\mathcal{E} = \frac{M_A}{2} v_A^2 \tag{22}$$

when the bunching performs the spatial displacement is any direction then we have

$$\mathcal{E} = \frac{M_A}{2} \frac{\ell^2}{T^2}, \tag{23}$$

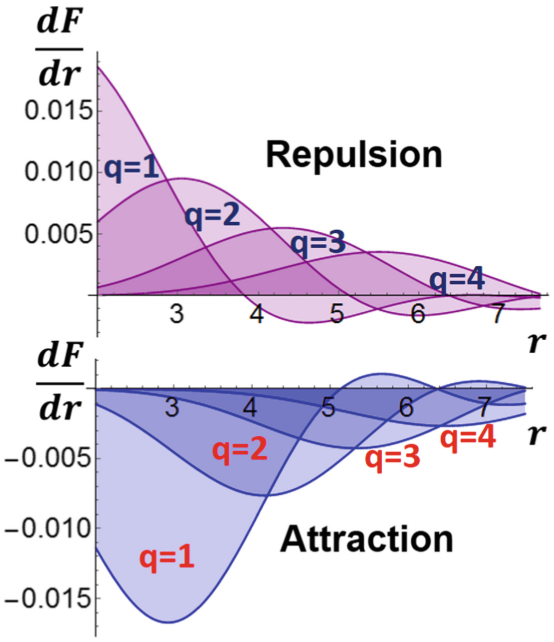

Fig. 3. The rate of change of electric force per radial distance for both scenarios: repulsion (up) and attraction (down). The plots are done up to the fourth order of the Bessel functions.

we focus now on the quantity T that is also seen as the time or period by which the bunching is displaced a length ℓ. Thus in a first instance the AER as function of the mass of albumin per unit of time can be expressed as

$$\text{AER} = \frac{2\mathcal{E}T}{\ell^2} \tag{24}$$

inserting Eq. 20 then AER is read as

$$\text{AER} = \frac{2\mathcal{E}}{\ell^2}\pi r\sqrt{\frac{2m_N\Delta r}{||\Delta \boldsymbol{F}(r,t)||\mathcal{A}}} \tag{25}$$

and the $\mathcal{C} = 2\pi r$ the circumference that defines the area occupied by the pass of the bunching of albumin through the glomerulus, then one gets that

$$\text{AER} = \frac{\mathcal{C}}{\ell^2\Delta r}\sqrt{2m_N\Delta r||\Delta \boldsymbol{F}(r,t)||\mathcal{A}} \tag{26}$$

that constitutes the theoretical equation of AER in humans due to the anomalous transit of albumin proteins through the kidney targeting the urine formation zone.

5.2 Numerical Approximations

The peaks of the electric force as shown in Fig. 2 (middle) yields the value: 0.7 for $\mathrm{r} = 2.0\,\mu\mathrm{m}$ and $3.0\,\mu\mathrm{m}$ for instance. It is interpreted as the maximum value of proteins excretion. Now we pass to estimate the AER from these values. For this end, we use the expression

$$\mathrm{AER} = \frac{\mathrm{M_{PR}}}{v_{\mathrm{PR}} \times s} \times \mathrm{V_{TOT}} \times \mathrm{Exp}\left[-\left(\frac{I - I_0}{\Delta I_0}\right)^2\right] \tag{27}$$

where $\mathrm{M_{PR}}$ mass of protein of albumin, $\mathrm{V_{TOT}}$ total volume for both kidneys, and v_{PR} full volume of proteins. We have introduced the Gaussian profile $\mathrm{Exp}[-\left(\frac{I-I_0}{\Delta I_0}\right)^2$ where is assumed that the AER value is depending on the capability of the nano device to get a precise value of the intensity of the electric force I_0. Since one expects that the nano device will be sending in average 90 K pulses/h then the error is set in a first instance to 10^{-4} Firstly, we assume that the net number of human glomerulus is 10^6 (both kidneys). Thus, we can estimate $\mathrm{V_{TOT}} = 0.7\ 64\ (10\,\mu\mathrm{m})^3\ 10^6$, where $0.7 = p_\ell$ denotes the estimated of the peak of electric force as seen in Fig. 2 and ℓ the order of the Bessel function. On the other hand, $v_{\mathrm{PR}} = \pi(2\,\mathrm{nm})^2\ 2\,\mathrm{nm} = 8\pi\,(\mathrm{nm})^3$ (assuming a cylindrical geometry). Finally, $\mathrm{M_{ALB}} = 1{,}6\ (1\,\mathrm{nm})^3\,\mathrm{kg}$, which is the albumin's mass. A straightforward calculation, yields $\mathrm{AER} \approx 2.22\ (1\times10^{-9})\,\mathrm{kg/s}$, where $1\mathrm{n} = 10^{-9}$. This value is actually of order of 420 mg/day being greater that the setpoint established by the nephrologist of order of 300 mg/day. This clearly is perceived in somewhat as the very beginning of the DKD in patients having an older diagnosis of type-2 diabetes of order of 10 years in average and in conjunction with a poor self-care that might be a crucial cause of the beginning of the DKD.

5.3 The Error of AER Calculation

Because the AER is a composition of various terms being each one of different nature in the sense that a precise value might involve a certain uncertainty, so a full equation that enclose all possible sources of errors can be written as

$$\frac{\Delta\mathrm{AER}}{\mathrm{AER}} = \sqrt{\left(\frac{\Delta p_\ell}{p_\ell}\right)^2 + \left(\frac{\Delta \mathrm{V_{TOT}}}{\mathrm{V_{TOT}}}\right)^2 + \left(\frac{\Delta \mathrm{I_0}}{\mathrm{I_0}}\right)^2 + \left(\frac{\Delta \mathrm{M_{ALB}}}{\mathrm{M_{ALB}}}\right)^2} \tag{28}$$

where the main source of error would come from the capacity of the model to make predictions of peak of the electric force sensed by the nano device. However the error can also be subject to systematic errors by the assumptions of the theoretical model. A rapid calculation of ΔAER yields 6%, roughly.

Figure 4 displays various scenarios where the intensity of the electric force as given by Eq. 15 are plotted. We can see the existence of a white and yellow area denoting the signal as seen by the nano sensor. We use the technique of Smooth-Density-Histogram and bandwidth methodology: top, middle and bottom: 0.10, 0.15 and 0.3 respectively. Top middle and bottom left plots would display what we can be sensed by a nano sensor.

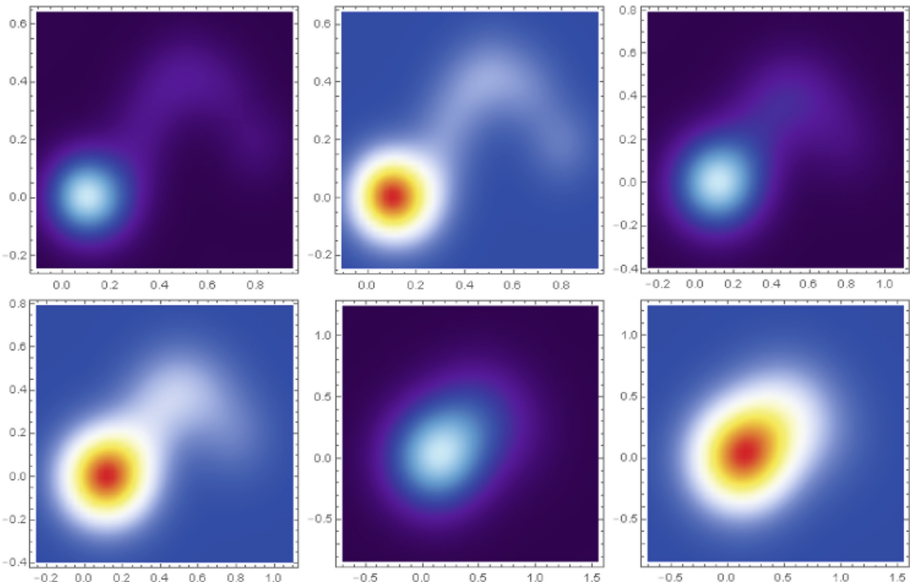

Fig. 4. Smooth-Density-Histograms for different scenarios of the intensity of electric force by using Eq. 10. Plots were done with the Smooth-Density-Histogram and bandwidth methodology: top, middle and bottom: 0.10, 0.15 and 0.3 respectively. The centers of plots denote the spatial location of the signal: albumin protein whereas their tails are associated to noise or another type of protein. The expected nano sensor would register data solely from the centered concentration as a first sign of a possible anomalous event in the renal apparatus. (Color figure online)

6 Conclusion

In this paper we have developed a theory that would estimate the AER a parameter of importance to make a accurate diagnosis of the renal disease in those type-2 diabetes patients. We turned to the territory of the Nanomedicine in the sense that we have proposed a technique that would identify the first phases of diseases as well as a method of surveillance through nano sensors has been explained. Since albumin are negatively charged proteins, it open the possibility to detect them with electric interactions governed by physics laws. Numerical estimations have yielded a crude estimate of 90 K pulses per hour being enough statistics to perform analysis of signal and noise acceptation and rejection, fact the one would help to nephrologist to reconfigure the treatment. The compound is understood to be a bunch of proteins of albumin. These giant proteins are leaving the glomerulus because their electrodynamics with the shielding of charges over the inner and outer layers of glomerulus. When the maximum value of the density of charge or compound is estimated, it enters in a straightforward estimation of AER, yielding a value of 450 mg/day. According to the clinical tests, this value belongs to the case of a type-2 patient showing the very beginning

of the DKD. These results would support the idea that the deployment of a nano sensor near to the glomerulus might be advantageous for the anticipation of the very beginning of DKD, by assuming the central hypothesis: dynamics of the bunches of albumin is entirely governed for repulsion and attraction electric forces.

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