Probabilistic Molecular Internalization in Tumors Based in Diffusion Equation and Electrodynamics

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***Abstract*—The action of internalization of drug delivery is seen as a three-phases event starting with the probability of arrival by which it is expected that a large fraction of cargos containing cytotoxic drugs can reach a tumor. With a fraction of them having arrived to tumor, electrical interactions would dictate the entrance or rejection of them. Thus, the ones that have could pass are depending on diffusive laws, thus the diffusion equation applies well. From all this, a theoretical model is build as well as computational simulations are presented and discussed.**

I. Introduction

A challenging route that should be taken the practitioners of the so-called targeted drug delivery (TDD) system [1] as well as the advanced magnetic drug targeting is the optimal management of toxicities and drug-drug interactions in both short-term as well as long-term periods. Clearly these points must be emphasized in all those patients with a high sensitivity to new drugs due to the diverse levels of potential complications would have in each phase of therapy. In this manner the implications from a long-acting doses and frequency should be deeply understood in order to characterize the reaction of patients to sophisticated treatments. Akyildiz in [2] has studied propagation and statbility of delivery systems. With the progress of novel materials in the field of nanotechnology, a wide spectrum of nanoparticles have emerged. Most of them have shown an interesting prospectiveness in the technique of TDD in the sense that their usage to attack tumor-based diseases have been seen as an effective and promising methodology in the modern Oncology.

In this letter, attention is paid to the physics aspects of delivering of nanoparticles sent through the bloodstream in which most of them would exhibit both chemical and physics interactions by degrading the quality of method [3]. In essence, the point whether nanoparticles-based delivery is either deterministic or probabilistic, is examined. Thus the main aspect that is emphasized in this letter is that of conjunction of various facts that might be behind of dynamics of nanoparticles when are traveling along the bloodstream towards to a concrete target such as a tumor [4]. As sketched in Fig.1, once the nanoparticles have been injected clearly one can expect diffusion of them so that the entire supplied volume of drugs behaves in according to the diffusion equation. Nevertheless, Fokker-Planck [5] can also be exhibited by them, so that all those nanoparticles experiencing a kind of drag forces might be seen as the missed dose. Along their trajectory, drugs can face

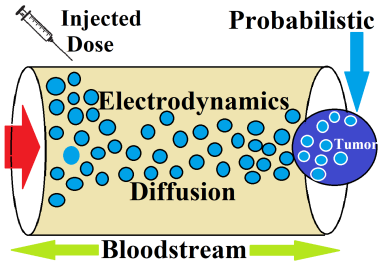

Fig. 1. Sketch of an even of targeted drug delivery after the injection of dose consisting in the electrodynamics, diffusion and probability at the entrance of nanoparticles into target tumor.

the presence of albumin so that interactions would minimize the success probability to some extent [6]. In this manner a natural question emerge? Which realistic percent of sent volume of drugs can arrive to tumor? To answer this question, it is necessary to translate the process of drug delivery to a combined scenario where diffusivity and electrodynamics can describe the pass of nanoparticles in the bloodstream. Moreover, the arrive of nanoparticles to tumor can be governed by probabilistic rules more than deterministic. In this manner, it is feasible to incorporate probability in a theory that is constructed in the ground of diffusion and Coulomb's forces [7]. Therefore, a crude description of internalized number $n_{\rm INT}$ of nanoparticles into tumor can be written by:

$$n_{\rm INT} = \frac{n_a}{n_e + n_r} \tag{1}$$

with n_a the ones that have arrived and n_e + n_r=$n_{\rm SEN}$ the total sent as the sum of that have had electrical interactions n_e that also are subject to diffusion along the bloodstream and n_r the number of rejected probabilistically nanoparticles. In second section, a probabilistic approach is presented. In third and fourth section, the electrical and diffusive descriptions are designed. Finally, simulations ans conclusion of this letter are presented.

II. Delivery Based in Probabilities

The success of an event of drug delivery can be measured in terms of number of nanoparticles that have been internalized into target tumor. Consider n nanoparticles (NPs) sent through the blood stream at the time t. It is expected that in a subsequent time $t+t_M$ a fraction of them can arrive to tumor.

In fact, only a part of them arrives to target due to interactions with cells and proteins, etc, [8]. Thus the efficiency of delivery can be written as:

$$E(t) = \frac{n_{\rm AR}(t)}{n_{\rm FR}(t) + n_{\rm RE}(t)} \tag{2}$$

with $n_{\rm AR}(t)$, $n_{\rm FR}(t)$ and $n_{\rm RE}(t)$, the number of effective nanoparticles that have arrived to target, the number that are free of interactions, and the number that have had chemical or electrical rejection along their path to tumor, respectively. It should be remarked that $n_{\rm FR}(t) + n_{\rm RE}(t) = n_{\rm TO}$ the total number of injected nanoparticles. Eq.2 can be seen from another angle in the sense that this efficiency abandons its deterministic status and departures to a probabilistic territory. In this manner, one can write down that:

$$E(t) = \frac{1}{\frac{n_{\rm AR}(t)}{n_{\rm FR}(t)}\left[1 + \left(\frac{n_{\rm RE}(t)}{n_{\rm FR}(t)}\right)\right]}. \tag{3}$$

Under the assumption that $\sum_m 1/m!\,(\frac{n_{\rm RE}(t)}{n_{\rm FR}(t)})^m = 0$ for $m \geq 2$ then Eq.3 can be again written as:

$$E(t) = \frac{n_{\rm AR}(t)}{n_{\rm FR}(t)}\left[{\rm Exp}\left(-\frac{n_{\rm RE}(t)}{n_{\rm FR}(t)}\right)\right]. \tag{4}$$

The negative exponential might be seen as a pessimistic scenario in which the efficiency falls down in time so that the entire process of drug delivery would be in risk. In fact, biochemical compounds and proteins like albumin would decrease the chance to maximize the efficiency of sent doses. In this manner, it is strongly desired that such efficiency exhibits at least a maximum value. In other words one might be suggesting that the efficiency behaves as a peaked distribution [9]. To accomplish this, one can establish for instance that: $\frac{n_{\rm RE}(t)}{n_{\rm FR}(t)}$=$\beta t^{\ell}$ so that from Eq.4 one has below:

$$E(t) = \frac{n_{\rm AR}(t)}{n_{\rm FR}(t)}\left[{\rm Exp}\left(-\beta t^{\ell}\right)\right], \tag{5}$$

by which one can recognize the case of ℓ=2 as the Gaussian profile. But of course it would not be the only one probabilistic manifestation of an event of drug delivery [10]. In fact one can impose additional restrictions under the dependence of time in order to give a shape to a known probability distribution function in the sense that:

$$\frac{n_{\rm AR}(t)}{n_{\rm FR}(t)} = \alpha t^{\ell-1}. \tag{6}$$

The direct consequences of Eq.6 turns out to be:

$$n_{\rm AR}(t) = \frac{\alpha}{\beta}\frac{n_{\rm I}(t)}{t} \Rightarrow n_{\rm RE}(t) = \frac{\beta t}{\alpha} n_{\rm AR}(t) \tag{7}$$

By putting Eq.6 into Eq.5 one gets:

$$E(t) = \alpha t^{\ell-1}\left[{\rm Exp}\left(-\beta t^{\ell}\right)\right] \tag{8}$$

that takes the form of a Weibull distribution. Eq.8 express the fact that the efficiency of sent nanoparticles acquires a maximum for some values of free parameters α and β, that would trigger the peaks of distributions. Actually, one can also see from Eq.3 and Eq.6 a peaked distribution with ℓ=2 also known as the Lorentzian distribution can also be derived:

$$E(t) = \frac{\alpha t^{\ell-1}}{1+\beta t^{\ell}} \Rightarrow E(t)|_{\ell=2} = \frac{\alpha t}{1+\beta t^2}. \tag{9}$$

In order to establish a Gaussian distribution for this specific example (and not be generalized along this letter) it is needed to redefine that $\frac{n_{\rm AR}(t)}{n_{\rm FR}(t)}$=$\gamma$ a constant in time. Thus one from Eq.5:

$$E(t) = \gamma\left[{\rm Exp}\left(-\beta t^{\ell}\right)\right]. \tag{10}$$

To aggregate the space, one can see in Eq.4 that the space-time probability becomes realistic in the sense that it satisfies the physical dimensions if and only if $\beta t^{\ell} \Rightarrow (\beta t)^{\ell}$, so that one gets below:

$$E(t) = g(v,s,\ell)\left[{\rm Exp}\left[-\left(\frac{vt}{s}\right)^{\ell}\right]\right]. \tag{11}$$

with v the velocity of nanoparticle. Clearly any deviation on the trajectory of nanoparticle is translated in terms of precision of technique. The function $g(v,s,\ell)$ is not unknown. This can be derived from the flux of probability as:

$$F(t) = {\rm Exp}\left[-\left(\frac{vt}{s}\right)^{\ell}\right], \tag{12}$$

and the efficiency becomes the derivative of flux with respect to velocity:

$$E(t) = \frac{dF(t)}{dv} = \frac{\ell}{v}\left(\frac{vt}{s}\right)^{\ell-1}\left[{\rm Exp}\left[-\left(\frac{vt}{s}\right)^{\ell}\right]\right]. \tag{13}$$

It is noteworthy that $E(t)$ can associate again to a Weibull probabilistic distribution function. The Gaussian case can be derived in a straightforward manner as done above, now when ℓ=2, one arrives:

$$E(t) = \frac{dF(t)}{dv} = \frac{2t}{s}\left[{\rm Exp}\left[-\left(\frac{vt}{s}\right)^{2}\right]\right], \tag{14}$$

that can be perceived as a Weibull-like system opts by the state $\ell = 2$, it is the Gaussian event that is analogue to Lorentzian case. From previous equations derived above, the reader can check out that the efficiency of drug delivery in this probabilistic context can be tested from the rate:

$$\frac{n_{\rm RE}}{n_{\rm AR}} = \frac{t\beta^{\ell}}{\alpha}, \tag{15}$$

in this way, the delivery is successful if $\alpha >> t\beta^{\ell}$.

III. The Electrodynamics View

While nanoparticles are made of metals, the promising citrate-coated gold nanoparticles have shown to be stable in aqueous solution while they bear negative charge [11]. Thus, due to the surface electrically charge flip, repulsive forces can emerge, as well as them can constitute a kind of attractor volume of albumin proteins that are negatively charged proteins. It is the case of protein corona of gold nanoparticles. In this

manner, a deep description based in electrodynamics would complementary to built a theoretical model of targeted drug delivery based so far in probability. For instance, consider that the nanoparticles have a spheric shape with a surface charge density given by: $\sigma = q/4\pi r^2$. Thus, for a single nanoparticle the charge is written as $q = 4\pi\sigma r^2$. One can wonder if once the nanoparticles traveling along the blood stream loses its initial geometry [12], that means that the radius is varying in time. Then in this scenario $q(t) = 4\pi\sigma r^2(t)$. Thus, for a couple of nanoparticles, the corresponding Coulomb repulsion force with $\epsilon_{\rm B}$ the permittivity of blood, reads:

$$F = \frac{4\pi\sigma_1\sigma_2 r_1^2(t) r_2^2(t)}{\epsilon_{\rm B}{\rm R}^2} \tag{16}$$

and the electric work done to move a charge towards a displacement ${\rm R} + \mathbf{x}$ reads:

$$W = F\mathbf{x} = \frac{4\pi\sigma_1\sigma_2 r_1^2(t) r_2^2(t)\mathbf{x}}{\epsilon_{\rm B}({\rm R}+\mathbf{x})^2} = \frac{4\pi\sigma_1\sigma_2 r_1^2(t) r_2^2(t)}{\epsilon_{\rm B}R^2(1+\frac{\mathbf{x}}{R})^2}. \tag{17}$$

Eq.17 allows us to write below an energy distribution based on the well-known Boltzmann-Maxwell distribution with $\sigma_1 = \sigma_2 = \sigma$. If Eq.17 denotes the system energy, the distribution can be written as:

$$B(\sigma) = N\sqrt{\frac{\pi}{\sigma}}{\rm Exp}\left(-\frac{4\pi\sigma^2 r_1^2(t) r_2^2(t)}{kT\epsilon_{\rm B}R^2(1+\frac{\mathbf{x}}{R})^2}\right) \tag{18}$$

with N a normalization constant. In this manner, the charged surface might be producing in a inherent manner a probability of energy. The Boltzmann-Maxwell would exhibit in this concrete example a kind of Shannon's entropy so that an universal probability distribution function reads:

$$\mathcal{P}(\sigma) = \left[{\rm Exp}\left(-\frac{1}{N}\sqrt{\frac{\sigma}{\pi}}\frac{4\pi\sigma^2 r_1^2(t) r_2^2(t)}{kT\epsilon_{\rm B}R^2(1+\frac{\mathbf{x}}{R})^2}\right)\right]^{N\sqrt{\frac{\pi}{\sigma}}} \tag{19}$$

where the electric work becomes now a kind of entropy so that W=Log$\mathcal{P}$. On the other hand, the cargo of nanoparticles can contains net charge. Thus $q = \int \rho dV$. The Coulomb force is then written below as:

$$F = \frac{1}{4\pi\epsilon}\frac{\int\rho_1 dV_1\int\rho_2 dV_2}{(R+\mathbf{x})^2} = \frac{1}{4\pi\epsilon}\frac{\int\rho_1 dV_1\int\rho_2 dV_2}{R\left(1+\frac{\mathbf{x}}{R}\right)^2}. \tag{20}$$

By using the sum with the restriction $\sum_{p\geq 2}\frac{1}{p!}\left(\frac{\mathbf{x}}{R}\right)^p$=0, then one gets below:

$$1 + \frac{\mathbf{x}}{R} = 1 + \frac{\mathbf{x}}{R} + \sum_{p\geq 2}\frac{1}{p!}\left(\frac{\mathbf{x}}{R}\right)^p = e^{\frac{\mathbf{x}}{R}}, \tag{21}$$

so that Eq.20 can be written as:

$$F = \frac{1}{4\pi\epsilon}\frac{\int\rho_1 dV_1\int\rho_2 dV_2}{(R+\mathbf{x})^2} = \tag{22}$$

$$= \frac{1}{4\pi\epsilon R}\int\rho_1 dV_1\int\rho_2 dV_2 e^{-\frac{2\mathbf{x}}{R}}. \tag{23}$$

While the cargo have a spherical geometry (for example) then the volumetric integrals being then equals for both distributions but have their radius different each other and the repulsive force is then written as:

$$F = \frac{4\pi}{9\epsilon R}\int\rho_1(r_1,s,t)r_1^3 dr_1\int\rho_2(r_2,s,t)r_2^3 dr_2 e^{-\frac{2\mathbf{x}}{R}}. \tag{24}$$

Consider the scenario that the densities are only dependent on s and t then Eq.24 acquires a simplified form:

$$F = \frac{\pi}{9\epsilon R}\frac{(r_1 r_2)^4}{4}\rho_1(s,t)\rho_2(s,t)e^{-\frac{2\mathbf{x}}{R}} \tag{25}$$

$$= \frac{\pi}{9\epsilon R}\frac{(r_1 r_2)^4}{4}|\rho(s,t)|^2 e^{-\frac{2\mathbf{x}}{R}} \tag{26}$$

by which it was assumed that the pair of densities are described by same diffusion equation so that acquire approximately same solution, in other words: $\rho_1(s,t) = \rho_2(s,t)$=$\rho(s,t)$. It is evident the lack of information about the volumetric charge densities are missing, so that one requires a consistent mathematical formulation in according to the nanoparticles along the bloodstream. It is an argument to turn now to the usage of diffusive descriptions as shall be done below.

IV. Usage of Diffusion Equation

One can see that Eq.26 is incomplete because not any specific information of volumetric charge densities that are enclosing the charged nanoparticles. As sketched the central idea of this letter, the onces the cargo has been inyected, then it follows the diffusive phase along the bloodstream. This logically suggests to employ the diffusion equation [13] in its simplest representation (1-dimension) for densities of Eq.26:

$$\frac{d\rho}{dt} = D\frac{d^2\rho}{ds^2}. \tag{27}$$

It can be modified for our ends, so that: $\frac{d\rho}{ds}\frac{ds}{dt}$=$D\frac{d^2\rho}{ds^2} \Rightarrow \frac{d\rho}{ds} = \frac{D}{v}\frac{d^2\rho}{ds^2}$, where only the longitudinal displacement is considered more than the axial. Therefore Eq.27 can be written as $\frac{d^2\rho}{ds^2} - \frac{v}{D}\frac{d\rho}{ds} = 0$ yielding the closed-form solutions:

$$\rho(s) = a_1{\rm Exp}\left[\sqrt{\frac{v}{D}}s\right] + a_2{\rm Exp}\left[-\sqrt{\frac{v}{D}}s\right]. \tag{28}$$

With this Eq.26 can be written as:

$$F = \frac{\pi(r_1 r_2)^4 e^{-\frac{2\mathbf{x}}{R}}}{36\epsilon R}\left|a_1 e^{\left[\sqrt{\frac{v}{D}}s\right]} + a_2 e^{\left[-\sqrt{\frac{v}{D}}s\right]}\right|^2. \tag{29}$$

One can note that the time is embedded in velocity of cargo v.One can see that this electric force is that emerges as an inherent interaction between same sign nanoparticles in their flipping processes such as the gold nanoparticles as mentioned above. So that, one can rewrite the efficiency Eq.2 as function of this Coulomb-like force:

$$E(t)=\frac{\frac{\pi(r_1r_2)^4}{36\epsilon R}\left|a_{\rm AR}e^{\left[\sqrt{\frac{v}{D}}s\right]}+a_{\rm AR}e^{\left[-\sqrt{\frac{v}{D}}s\right]}\right|^2}{\frac{\pi(r_1r_2)^4e^{-\frac{2\mathbf{x}}{R}}}{36\epsilon R}\left|a_{\rm FR}e^{\left[\sqrt{\frac{v}{D}}s\right]}+a_{\rm FR}e^{\left[-\sqrt{\frac{v}{D}}s\right]}\right|^2+\frac{\pi(r_1r_2)^4e^{-\frac{2\mathbf{x}}{R}}}{36\epsilon R}\left|a_{\rm RE}e^{\left[\sqrt{\frac{v}{D}}s\right]}+a_{\rm RE}e^{\left[-\sqrt{\frac{v}{D}}s\right]}\right|^2} \tag{30}$$

where at the numerator $e^{-\frac{2\mathbf{x}}{R}}\approx 1$ since $\mathbf{x}=0$, the nanoparticles have reached their target. It should be noted that the coefficients of Eq.30 acquire their values in according to Eq.2 because it is evident that the number of nanoparticles is proportional to the charge densities.

V. Simulations and Conclusion

In Fig.2 simulations of Eq.30 are displayed. To accomplish these plots, crude estimations have been done. For example, in up panel, the numerator had the value of 1. It is compatible to the case with $s=0$ and $a_{\rm AR}\approx\frac{18\epsilon R}{\pi(r_1r_2)^4}$. At the denominator D has units of m^2/t then a crude estimate of $e^{\sqrt{t}\sin(x)}+e^{-\sqrt{t}\sin(x)}$ was used in both for free of interactions and the rejected ones. It is because the flipping property produces the simultaneity of attraction and rejection, so that a sinusoid relations applies well. In this way, the maximum value of efficiency has turned out to be of 12% that is favorable in the sense that a small efficiency translates as a poor Coulomb interaction among the nanoparticles so that one has the chance that a substantial fraction of them might be arriving to their target. In down panel, the case when the numerator in Eq.30 is replaced by a $\sin(x)$ is displayed. In addition at the denominator $e^{\sqrt{t}\sin(1.5x)}+e^{-\sqrt{t}\sin(1.5x)}$ was used. One can see that the arrows are pointing the values of a null efficiency of Coulomb forces against the propagation of nanoparticles. In fact, for distances 6.6 to 7.8 (a.u.) and for times of 2.5 (a.u.) one can see that the supposed nanoparticles are exhibiting a slow displacement that is free of Coulomb interactions. In contrast to other space-time zones, the fact that the nanoparticles are traveling fast, it might not be guaranteeing a optimal drug delivery, instead it would be degrading the displacement of cargo to the extent of having Coulomb-like interactions. Therefore, the approach probabilistic in conjunction to a theory of electrodynamics and diffusion equation, has yielded that the displacement in cylindric spaces (vessels for example) would contain physics based in Coulomb forces, so that the arrival of nanoparticles to the target will be delayed and are potentially rejected because the self-forces among the bunches of charged electrically nanoparticles.

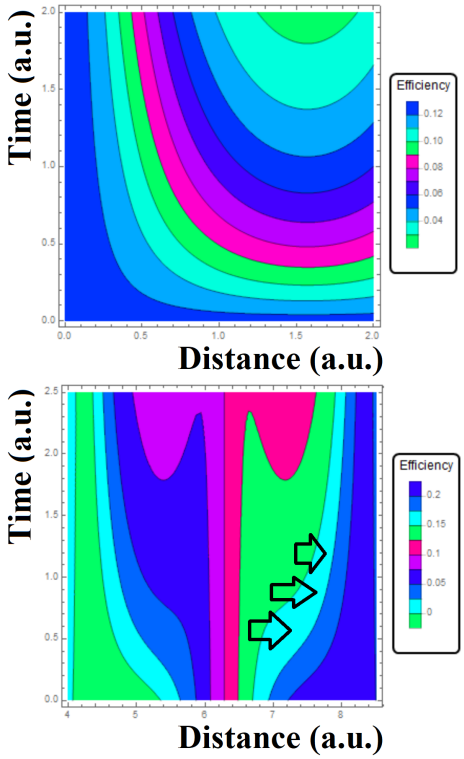

Fig. 2. Top: the case when $\mathbf{x}=0$. Down: the case with a $\sin(\mathbf{x})$ approximation displaying zones of a null efficiency of Coulomb-like fields at the injected charged nanoparticles Plots were done with package of Ref. [14].

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