Interesting Details about Diffusion of Nanoparticles for Diagnosis and Treatment in Medicine by a New Analytical Theoretical Model

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Abstract: In recent years diagnosis and treatment in medicine have important advantages by the use of nanoparticles. Of great interest results the modality, with which they diffuse into the human body, and/or in specific human organs; the diffusion is indeed one of the three most important parameters for transport processes in solid state physics and soft condensed matter, also at nanolevel. A new appeared analytical "time-domain" Drude-Lorentz-like model for classical, quantum and relativistic transport in nano-systems is demonstrating high generality and good fitting with available experimental literature data. The range of application is very large, due to a gauge factor inside the model, comprehending all sectors of medicine. An interesting analysis related to the diffusion of nano-substances in the human body through nanoparticles indicated in nanomedicine is considered in this paper.

Keywords: Diagnosis, Treatment, Nanomedicine, Nano-bio-technology, Theoretical modelling, Diffusion.

INTRODUCTION

Nanomedicine is concerned with the medical application of the opportunities arising by nanotechnology; it deals with all knowledges and technologies having a medical utilization in the order of magnitude of nanometers (1-100 nm). Working at this scale, nanotechnology changes the traditional distinction between biology, chemistry and physics, constituting a bridge of fruitful interdisciplinarity [1,2]. The nanotechnology applications are ranging from the medical use of nanomaterials to the formulation of new drug delivery systems, from nano-bio-sensoristics [3] to the use of molecular nanotechnology.

Nanomedicine aims to provide a set of research tools and clinically helpful devices for the near future [4]. The "speculative" molecular nanotechnology believes that cell repair machines will be able to revolutionize medicine. In this perspective, the technological application of nanotechnology in medicine represents an application method of molecules discovered by genomics and proteomics.

Currently this field is in constant evolution at global level, in relation to the application developments, to the deep understanding of toxicity and environmental impact of nanomaterials, and to the connected theoretical mathematical modelling.

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ADVANTAGES OF THE USE OF NANOTECHNOLOGY IN PHARMACOLOGY

Nanoparticles have unusual properties, which can be utilized for modifying the kinetics of drugs. The theoretical advantages are multiple:

a) high solubility;

b) longer duration of drug exposure;

c) the exposure of drug, trapped in the nanoparticle, in the target site;

d) a greater therapeutic index;

e) the potential to develop less resistance for the chronic use [5].

Complex systems of drug distribution have been developed, including the ability to cross the cell membrane and cytoplasm. Pharmacologic implantable drug distribution can avoid peaks and tails at low hematic dosage and should reduce the collateral effects. Nanoparticles have been shown to be able to pass the hematic-brain barrier without particular difficulties, and then to act as a carrier for hydrophobic and hydrophilic drugs. The strength of a system of absorption or distribution of drugs is also its ability to alter the pharmacokinetics of drugs [6].

Nanomedicine can work with high specificity, using in particular two possible methods for increase the specificity:

a) a passive method, related to an increase of mass vascularization, which permits a greater presence on target tissues;

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b) an active method, with the use of probes to which drug molecules are bound.

Another important feature is the "triggered response"; the medications are placed inside the human body and act only to the appearance of a particular signal acting as activator.

Nanoparticles, able to heat up when placed in a magnetic field and attached to active molecules such as drugs, are designed. This complex is injected in body; when the nanoparticles have reached the target organ, a selective magnetic field is activated. In this way it is possible to obtain a local release of drug [7].

These advances lead to interesting improvements, particularly in the field of diagnosis and rapid controlled treatment, if also supported by a proper theoretical modelling.

NANOMATERIALS FOR THE VEHICULATION OF SUBSTANCIES IN HUMAN BODY

The possibility of binding some markers to various kinds of nanoparticles, such as nanoshells, dendrimers, liposomes, for recognizing types of cells, such as cancer cells, is a primary object of the current research. Among the possible markers we remember:

a) the folic acid, present in all cells, but mainly in tumoral cells;

b) integrin αvβ3, present in the cells of tumor vessels. Considering all β3 integrins, the "αvβ3" is a receptor capable of binding vitronectin, fibronectin, osteopontin and trombospondin [8, 9].

Among the possibilities to use peculiar nanomaterials with specific characteristics, particular attention is given to:

a) Nanoshells: it has been demonstrated that the use of gold (silver)-coated nanoshells can kill cancer cells in mice. Nanoshells are thin metal shells with typical thickness of a few nanometers, containing a dielectric core. Due to this structure, they have both chemical and optical special properties. The variation of the size and the core involves the precise variation of the optical resonance of these particles with precision in a wide range, between ultraviolet and the mid-infrared [10].

b) Quantum dots: Q-dots are nanocrystals with measure of order of the volume of a protein, which have the property of emitting fluorescence in nearly all colors; they can be used as probes for highlighting determined reactions in cells, because of detecting minimum quantities of a given molecule. They are available in an almost unlimited range of colors, that can be customized by changing the particle size or composition.

c) Fullerenes: molecules composed of carbon atoms, are "*in vivo*" a powerful antioxidant with no acute toxicity [11]. Some authors have also shown a protective activity on neurons, in particular a reduction activities of axonal damage in mice with multiple sclerosis [12]. A single particle is tied to the end of a carbon nanotube and the vibrational frequency of the nanotube with and without the particle is measured; the difference between the two frequencies allow the measure of the mass of the enclosed particles. Chemical sensors using nanotubes for the measure of various properties of molecules in the gaseous state have been also designed.

d) Nanodiamonds: diamonds originating when a mixture of TNT/RDX (3/2) is subjected to a supersonic combustion (5 GPa, 2000 °C). Nanodiamonds surrounding a drug can carry the same drug, preventing the release of healthy cells, thus limiting toxic effects.

INTERESTING FEATURES BY A NEW ANALYTICAL MODEL FOR TRANSPORT AT NANOLEVEL

The functioning of the cardiovascular system can be explained using the physical principles related to the hydrostatics-hydrodynamics laws, although it has features that prevent a precise quantitative description.

Locally the flow is not continuous in the majority of vessels, but pulsatile. The circulatory system is branched and blood is a heterogeneous liquid (suspension of corpuscles in plasma), then with "non-Newtonian" characteristics.

Globally however, with exception of the microcirculation, the assumption of Newtonian viscosity can be considered valid for blood motion with theoretically evaluated errors in the order of 1-2%.

At electric level, it exists a standardized symbology for the synthetic representation of resistive, inertial and accumulation phenomena, which adequately joins the description in hemodynamic terms. It is therefore frequent and productive the use of the electric analogy for representing phenomena related to mass (volume)

transport, considering a motion which keeps into account of elastic and viscous effects [13-15].

Recently it has been performed a new analytical model generalizing the Drude-Lorentz model, which is one of the most utilized models for transport processes in solid state physics and soft condensed matter [16]. It provides analytical time-dependent expressions of the most important quantities related to the transport processes, i.e.:

a) the velocities correlation function $<\vec{v}(t)\cdot\vec{v}(0)>_T$ at temperature *T*, by which the velocity of a nanoparticle at time "*t*" is obtainable;

b) the mean squared deviation of position $R^2(t)=\left\langle[\vec{R}(t)-\vec{R}(0)]^2\right\rangle$, by which the position of a nanoparticle is obtainable;

c) the diffusion coefficient *D*, which gives interesting information about the propagation in time and space of a nanoparticle [7, 17, 18].

With this model it is possible both to fit experimental results and also to find new characteristics and details for experimental confirmation; it contains also a gauge factor, which permits its use from sub-picolevel to macrolevel.

Following the time-dependent perturbation theory, analytical calculation lead to relations for the velocities correlation function, the mean square deviation of position and the diffusion coefficient of carriers moving in a nanostructure. Considering the quantum level, factors incorporating the quantum behaviour are the weights f_i, related to plasma frequencies by:

$$\omega_{p_i}{}^2=\frac{4\pi N e^2}{m}f_i\,, \tag{1}$$

where *N* is the carrier density, *m* and *e* respectively the mass and the charge of the carrier.

Both in the classical and in the quantum version, the general calculation is performed *via* contour integration, determining the integral by the poles of the real part $\mathrm{Re}\,\sigma(\omega)$ of the complex conductivity $\sigma(\omega)$ in the complex plane. After calculation of the expression of the velocities correlation function, it is possible to calculate the mean square deviation of position considering the relation:

$$R^2(t)=2\int_0^t dt'\left(t-t'\right)\left\langle\vec{v}(t')\cdot\vec{v}(0)\right\rangle, \tag{2}$$

and the diffusion coefficient, defined in the usual way as

$$D=\frac{1}{2}\frac{d}{dt}R^2(t)\,. \tag{3}$$

The diffusion coefficient *D* related to the new model has the following quantum analytical expressions:

$$D=2\left(\frac{KT}{m^*}\right)\sum_{i=0}^{n}\left(\left[\frac{f_i\tau_i}{\alpha_{iR}}\sin\left(\frac{\alpha_{iR}}{2}\frac{t}{\tau_i}\right)\exp\left(-\frac{t}{2\tau_i}\right)\right]\right) \tag{4}$$

$$D=\left(\frac{KT}{m^*}\right)\sum_{i=0}^{n}\left(\left(\frac{f_i\tau_i}{\alpha_{iI}}\right)\left(-\exp\left(-\frac{1+\alpha_{iI}}{2}\frac{t}{\tau_i}\right)+\exp\left(-\frac{1-\alpha_{iI}}{2}\frac{t}{\tau_i}\right)\right)\right) \tag{5}$$

The parameters α_{hK} of the model are two real numbers defined in this way:

$$\alpha_{iR}=\sqrt{4\tau_i^2\omega_i^2-1} \tag{6}$$

$$\alpha_{iI}=\sqrt{1-4\tau_i^2\omega_i^2} \tag{7}$$

with τ_i and ω_i relaxation time and frequency of each mode respectively, corresponding to the various weights in the superposition of the states, and m^* the effective mass of the carrier.

The classical expressions of Eqs (4-7) have $f_i=1$, $\tau_i=\tau$ and $\omega_i=\omega_0$ [7, 17, 18].

RESULTS AND DISCUSSION

It has been considered four nanomaterials of great interest in nanomedicime, i.e. CTNs, Au, Ag, C, studyind the behaviour of their diffusion. About the other used values, it has been fixed the temperature $T=310\,K$, two values of the parameter α_I (0.1 and 0.9), an average relaxation time $\tau_{av}=10^{-13}\,s$ and values of m^* as resumed in Table **1**. The relaxation time in simple liquids takes indeed values of order of $10^{-12}-10^{-14}\,s$. Materials constituting the soft condensed matter (as blood) have intermediate properties between solid and liquid, and combine elastic and viscous response.

Figures **1-4** present the variation of the diffusion in time for the considered nanomaterials. Note that the variation of the parameter α_I implies also a variation

of the shape of diffusion, because of the appearance of α_I in the arguments of exponentials of Eq. (5).

Table 1: Values of Effective Masses m^* for the indicated Nanomaterials (m_e = mass of electron).

Nanomaterial	m^*
CTNs [19]	0.5 m_e
Au [20]	1.1 m_e
Ag [21]	1.15 m_e
C [22]	1.66 m_e

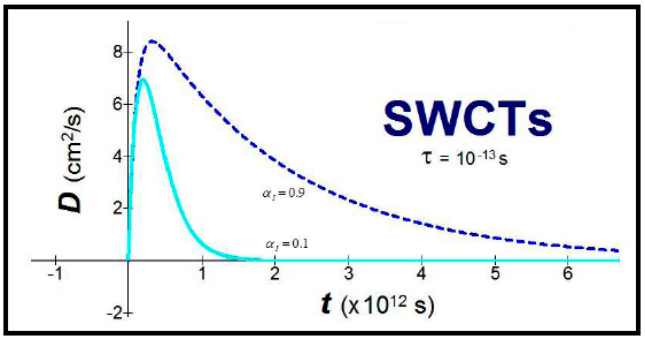

Figure 1: *D* vs *t* for single walled carbon nanotubes.

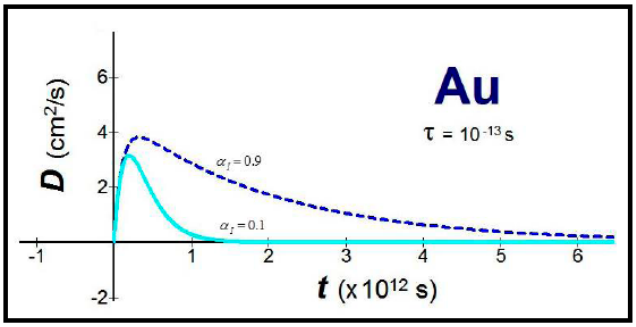

Figure 2: *D* vs *t* for nanogold.

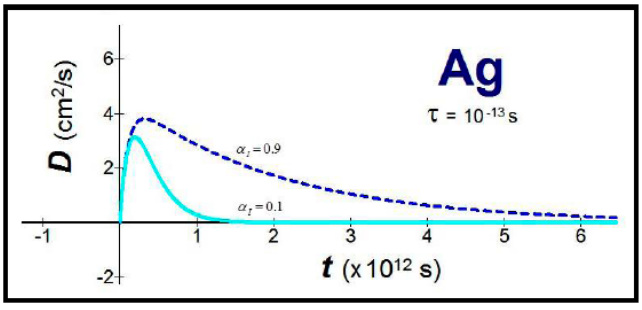

Figure 3: *D* vs *t* for nanosilver.

Table **2** resumes the peak values of diffusion, as determinable by figures, for the two values of α_I respectively.

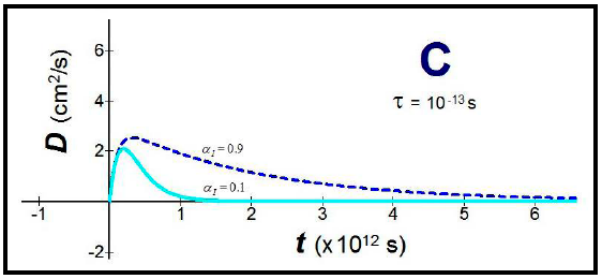

Figure 4: *D* vs *t* for nanodiamond.

Table 2: Peaks in Diffusion considering $\alpha_I = 0.9$ (D_1) and $\alpha_I = 0.1$ (D_2), for the considered Nanomaterials

Nanomaterial	D_1 (cm²/s) ($\alpha_I = 0.9$)	D_2 (cm²/s) ($\alpha_I = 0.1$)
CTN	8.44	6.90
Au	3.87	3.13
Ag	3.84	3.12
C	2.54	2.07

CONCLUSIONS

In this work it has been considered the application of a new analytical dynamics model to nano-substances, injectable in the human body, through a study of their diffusion. The model was built following the time-dependent perturbation theory, but it presents the new characteristics to offer analytical expressions of the most important transport parameters, thanks to the possibility of performing a complete Fourier transform of the complex conductivity $\sigma(\omega)$ [17, 18].

The model holds both for the motion of carriers inside a nanostructure, as studied in this work, and for the motion of nanoparticles inside the human body, because it contains a gauge factor, which permits its use from sub-picolevel to macrolevel.

The possibility to have informations about diffusion is an important information in general in nanomedicine and in particular for diagnosis and treatment.

The model offers interesting new peculiarities of nano-transport, so as the confirmation of existing results, previously found through important transport models, like Drude-Lorentz and Smith models.

Considerable points concerning the obtained results can be underlined:

1) the particular choice of nanomaterial is reflected in a variation of the diffusion in time, so as on its peak;

2) other possibilities in the direction of a required variation of diffusion regard temperature, the

variation of the effective mass through the doping and in connection to the chiral vector [23], the variation of the parameter α_I of the model, which is a function to the frequency and the relaxation time [17];

3) the importance of the study of these parameters at nanofabrication level for nanomedicine [24];

4) the versatility of the model, useful in both ways:

a) for creating new devices with desired characteristics;

b) for testing and/or obtaining new parameters values by existing experimental data [25].

The rapidity of answer for nanomaterials travelling in the human body and inside nanostructures is very important for a fast diagnosis of possible diseases/dysfunctions, resulting in the possibility of a rapid treatment.

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