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Fractional diffusion of membrane receptors in endocytosis pathway

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Abstract. In this paper the diffusion model representing the motion of membrane receptors with respect to virus endocytosis is considered in the context of applied mechanics. The unexpected behaviour of the receptor density that moves from higher concentrations in the unbound phase to lower concentration at the right of the virus surface is accounted for introducing a mechanical drift term in the governing equation so that the difference of concentrations, higher in the bounded phase and lower in the unbounded phase is accounted for in the receptor motion. Additionally, a non-gaussian model of diffusion has been introduced in terms of fractional generalization of the Fick law.

Introduction

Endocytosis is one of the main processes by which the cells of the human body receive substances and nutrients from the extracellular matrix, but it is also the route whereby viruses enter host cells to reproduce [1,2]. Generally, viruses have protuberances, small spikes, called ligands, on their outer surface. Ligands play a major role in the first phase of endocytosis, because they are responsible for the first contact by the virus with the cell membrane. The ligands form bonds with membrane receptors, which diffuse under the virus, to the area where endocytosis will occur, to allow the formation of various ligand-receptor pairs. As the virus descends toward the membrane, and more ligand-receptor pairs are formed, it exerts pressure on the membrane, deforming it. So, when the entire surface of the virus is in contact with the membrane, a concavity will have been formed in which the virus will reside. This last mechanism is called invagination and is completed as soon as the entire virus is surrounded by the cell membrane and passes the plasmalemma finding itself in the cytosol. Such a foreign body in the cell is called an endosome. This process will be followed by dissolution of the endosomatic capsule and biosynthesis of the viral components.

It's very important to know the time it takes viruses or nanoparticles to permeate the membrane, because on the one hand a virus that spends too much time to cross membrane will not be able to infect the host body, and on the other hand drug-containing nanoparticles can be functionalized more optimally to form ligand-receptor bonds effectively and act faster.

Recently the fractional calculus tool has provided excellent results to describe tissue biomechanics [3,4], proving its usefulness in describing tissue behaviour.

The aim of this paper is to propose a model that describes receptor diffusion, through a fractional form of Smoluchowski's fractional equation, which considers not only the chemical potential, given by Fick's law, but also an external potential in term of Morse potential.

The gaussian diffusion of membrane receptors

The mathematical formulation of the Stefan' problem proposed in previous section is not satisfactorily, from a mechanical perspective for the following reasons: i) The motion of the

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receptors following diffusion is always in the direction of the lower concentrations; ii) In order to achieve condition i) a first-order singularity in concentration appears at the moving boundary separating the bounded-unbounded phases of the receptors; iii) The force-flux relation presented by the Fick relation involves a random motion of diffusion of particles, non-mutually interacting, in a viscous media. This condition is hardly to find in receptors floating in the cell-membrane since the presence of other larger molecules of cholesterol, rafts and large protein-channels may be observed in real cellular membranes.

The aforementioned considerations pushed the authors, toward a different model of receptor diffusion that make use of the generalization of the Fick law with the introduction of fractional calculus [5,6,7,8,9]. In this regard, in the present section the first two issues i) and ii) will be considered introducing a mechanical drift in the model, derived from a specific potential, that represent the driving force that allows to overcome the hole of concentrations among the bounded-unbounded phases of the receptors. This potential represents an electrostatic attraction among the OH- sites of the receptors and the H+ protons free to connect in the virus ligands and, for them, a specific expression of potential has been chosen in the following. Let us consider a generic instant when the virus has already made first contact with the membrane:

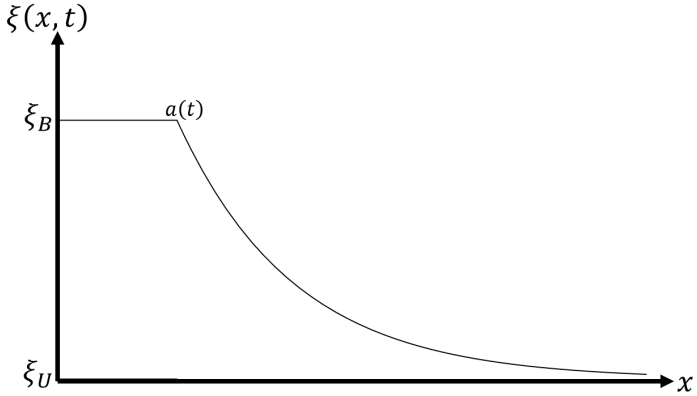

Fig. 1. Schematic representation of the receptor density profile of the proposed model.

Receptor diffusion follows Fick's classic law, in which there is an additional term:

$$j(x,t) = -\lambda \frac{\partial \xi(x,t)}{\partial x} - \frac{\xi(x,t)}{\zeta} \frac{dU(x)}{dx}. \tag{1}$$

Where $\lambda = \frac{k_B T}{\zeta}$ is the diffusivity coefficient $[\lambda] = \frac{L^2}{T}$, $\zeta = 4\pi\eta r$ friction factor $[\zeta] = \frac{M}{T}$, η membrane viscosity $[\eta] = \frac{M}{L\,T}$ e r radius of the receptor $[r] = L$. While $U(x)$ is the potential energy, which we decided to express through the following Morse potential:

$$U(x) = k_B T \left(1 - e^{-\sqrt{\frac{k_e}{2k_B T}}\,(x - a(t))}\right)^2. \tag{2}$$

Where k_e is the force at the minimum of the well. Contrary to the model [10], we assumed that we know the density of receptors at the interface. This density is the same as that found under the virus with regard to ligand-bound receptors, and we denote it by ξ_B. We also know the density of unbound receptors in areas far from where the process of endocytosis is occurring. We denote this density by ξ_U. Noting that $\xi_B > \xi_U$. Summarizing in mathematical terms, with reference to Fig. 1:

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$$\xi(x,t) = \begin{cases} j(x,t) = 0, \xi(x,t) = \xi_B & if \ \ x \leq a(t) \\ j(x,t) \to 0, \xi(x,t) = \xi_U & if \ \ x \to \infty \end{cases} . \tag{3}$$

To find the condition at the interface, we assume that over time the change in receptor density over the domain remains constant:

$$\frac{d}{dt}\left[\int_0^{a(t)} \xi(x,t)\, dx + \int_{a(t)}^{\infty} \xi(x,t)\, dx\right] = 0. \tag{4}$$

We apply Leibniz rule to (4) and taking into account the boundary conditions (3), we get:

$$\int_0^{a(t)} \frac{\partial \xi(x,t)}{\partial t} dx + \xi(a(t),t)\frac{da(t)}{dt} + \int_{a(t)}^{\infty} \frac{\partial \xi(x,t)}{\partial t} dx - \xi(a(t),t)\frac{da(t)}{dt} = 0. \tag{5}$$

We can elide the equal terms of (5) and since the density of receptors under the virus over time remains constant, we can erase the first integral, then:

$$\int_{a(t)}^{\infty} \frac{\partial \xi(x,t)}{\partial t} dx = 0. \tag{6}$$

Recalling the continuity equation: $\frac{\partial \xi(x,t)}{\partial t} = -\frac{\partial j(x,t)}{\partial x}$. We can substitute it into (6) and integrate:

$$[j(x,t)]_{a(t)}^{\infty} = 0. \tag{7}$$

The first term validated to infinity is null, while in the second term we have that the potential present a minin in $a(t)$ and therefore its derivative will be zero, so there remains only a single term:

$$\lambda \frac{\partial \xi(a(t),t)}{\partial x} = 0. \tag{8}$$

By deriving with respect to time the (8), the speed of the interface can be obtained:

$$\dot{a}(t) = -\frac{\frac{\partial \xi(a(t),t)}{\partial t \partial x}}{\frac{\partial^2 \xi(a(t),t)}{\partial x^2}}. \tag{9}$$

It is interesting to note that by adopting the form (2) of the Morse potential the diffusion of receptors is from higher to lower potentials, in this case that at the interface. Finally, we can write the complete system of the set of equations, in the form of Stefan's problem [11], describing the flow of receptors:

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$$\begin{cases} \dfrac{\partial \xi(x,t)}{\partial t} = \lambda_\beta \dfrac{\partial^2 \xi(x,t)}{\partial x^2} + \dfrac{1}{\zeta}\left(\dfrac{\partial \xi(x,t)}{\partial x}\dfrac{dU(x)}{dx} + \xi(x,t)\dfrac{d^2U(x)}{dx^2}\right) & (10.a) \\ \xi(a(t),t) = c_B. & (10.b) \\ \xi(x\to\infty,t) = c_U. & (10.c) \\ \dot{a}(t) = -\dfrac{\dfrac{\partial \xi(a(t),t)}{\partial t \partial x}}{\dfrac{\partial^2 \xi(a(t),t)}{\partial x^2}}. & (10.d) \end{cases}$$

The domain of the $(10.a)$ is $a(t) < x < \infty, t > 0$.

The fractional-order model of membrane receptors diffusion

We introduce the fractional Fick law in terms of the Caputo derivative [12] with $0 < \beta < 1$:

$$j(x,t) = -\lambda_\beta \left({}_0^C D_t^\beta \frac{\partial \xi(x,t)}{\partial x}\right)(x,t) - \frac{\xi(x,t)}{\zeta}\frac{dU(x)}{dx}. \quad (11)$$

In which λ_β is the anomalous diffusivity coefficient with dimensions: $[\lambda_\beta] = \frac{L^2}{T^{1-\beta}}$. $U(x)$ is as previously the Morse potential. For the condition at the interface, we can follow the steps given above up to equation (7). So, we get: $\lambda\left({}_0^C D_t^\beta \frac{\partial \xi}{\partial x}\right)(a(t),t) = 0$. Using property ${}_0 I_t^\beta \left({}_0^C D_t^\beta f\right)(t) = f(t) - f(0)$ and then deriving with respect to time and isolating the interface velocity, we obtain the same equation for the non-fractional system proposed before. To obtain the time-fractional diffusion equation, we substitute (11) into the continuity equation. The complete system will be:

$$\begin{cases} \dfrac{\partial \xi(x,t)}{\partial t} = \lambda_\beta \left({}_0^C D_t^\beta \dfrac{\partial^2 \xi}{\partial x^2}\right)(x,t) + \dfrac{1}{\zeta}\left(\dfrac{\partial \xi(x,t)}{\partial x}\dfrac{dU(x)}{dx} + \xi(x,t)\dfrac{d^2U(x)}{dx^2}\right) & (12.a) \\ \xi(a(t),t) = c_B. & (12.b) \\ \xi(x\to\infty,t) = c_U. & (12.c) \\ \dot{a}(t) = -\dfrac{\dfrac{\partial \xi(a(t),t)}{\partial t \partial x}}{\dfrac{\partial^2 \xi(a(t),t)}{\partial x^2}}. & (12.d) \end{cases}$$

Numerical investigation

For both system $(10.a - 10.d)$ and $(12.a - 12.d)$, it is not possible to obtain an analytical solution, so we applied the finite difference method. For simplicity we will report the case where $\beta = 0$ and then we get the non-fractional system again. Considering a generic particle with a diameter $d \cong 38\,nm$, the data used follow: $\eta = 10^{-3}\frac{pN\,\mu s}{nm^2}$, $r = 5\,nm$, $\zeta = 0.0628\frac{pN\,\mu s}{nm}$, $\lambda = 67.8\,\frac{nm^2}{s}$, $k_e = 0.01\,pN$, $c_u = 5\times10^{-4}\,nm^{-2}$,$c_B = 5\times10^{-3} nm^{-2}$. In the following graph, one can observe the curves obtained from the numerical solution for the receptor densities as a function of the radius of a generic virus for different times:

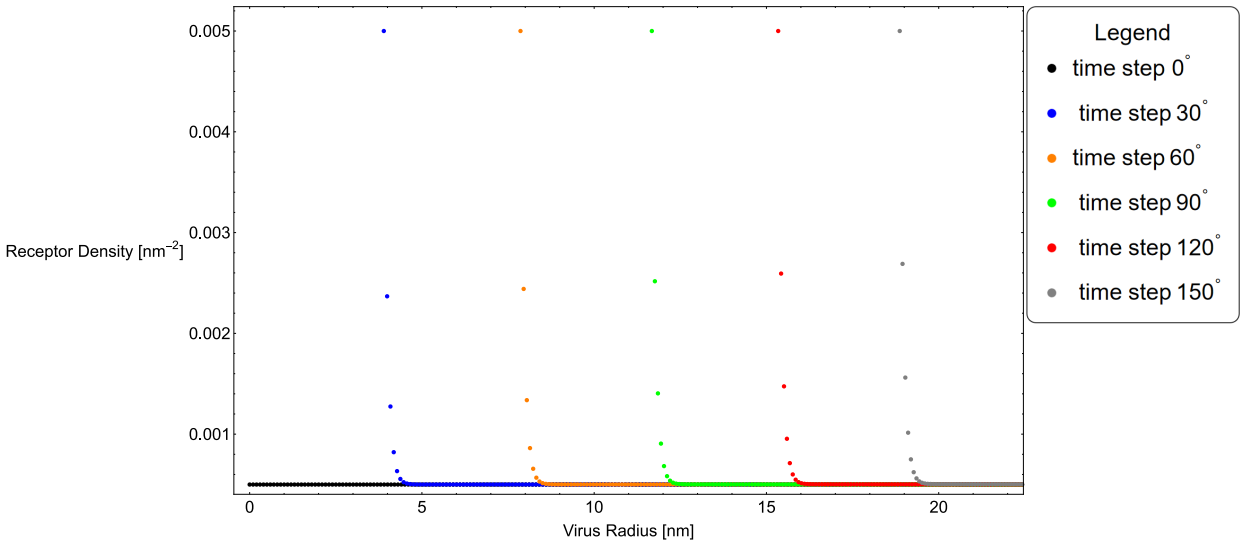

Fig. 2. Numerical solution of the proposed model with five curves at different time instants. The first point at the top of each curve represents the particle-membrane interface.

While in this second graph the corresponding interface position as a function of time. Each first point of the receptor density curves corresponds to one of the red curve points of the interface position.

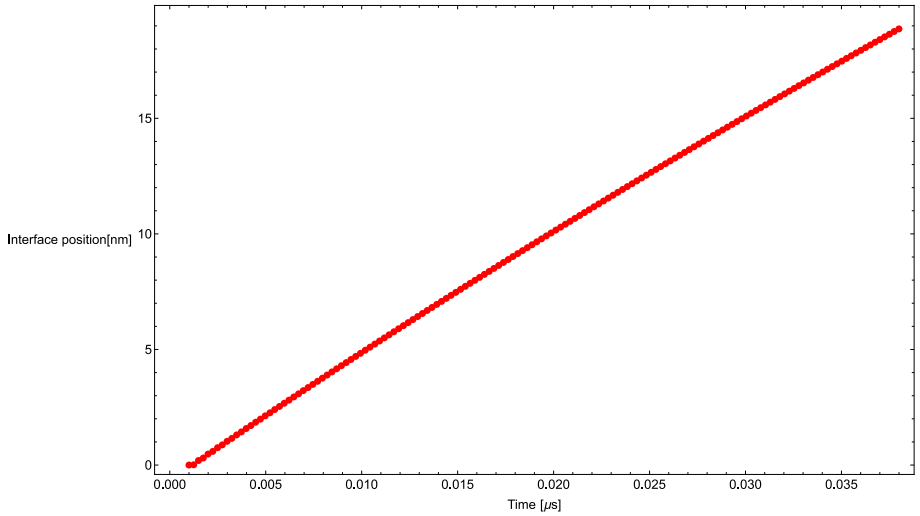

Fig. 3. Position of the particle-cell membrane interface as a function of time.

Conclusions

In this paper we analyzed the process of endocytosis and specifically the diffusion of receptors under the virus, an important step that allows the virus to bind to the cell membrane. We proposed a new model of receptor diffusion by considering an external potential as a function of the Morse potential. And finally proposed a generalized time-fractional form of the model, representing a typical sub-diffusive process, in which for $\beta = 0$ we regain the classical model.

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