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Q1 Fractional derivatives in the transport of drugs across biological materials and human skin

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HIGHLIGHTS

- Fractal derivatives can account for the transport in heterogeneous media.
- Two differently defined fractal operators are compared.
- Diffusion models based on a memory formalism approach.

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ABSTRACT

The diffusion of drugs across a composite structure such as a biological membrane is a rather complex phenomenon, because of its inhomogeneous nature, yielding a diffusion rate and a drug solubility strongly dependent on the local position across the membrane itself. These problems are particularly strengthened in composite structures of a considerable thickness like, for example, the human skin, where the high heterogeneity provokes the transport through different simultaneous pathways. In this note, we propose a generalization of the diffusion model based on Fick's 2nd equation by substituting a diffusion constant by means of the memory formalism approach (diffusion with memory). In particular, we employ two different definitions of the fractional derivative, i.e., the usual Caputo fractional derivative and a new definition recently proposed by Caputo and Fabrizio. The model predictions have been compared to experimental results concerning the permeation of two different compounds through human skin *in vivo*, such as piroxicam, an anti-inflammatory drug, and 4-cyanophenol, a test chemical model compound. Moreover, we have also considered water penetration across human stratum corneum and the diffusion of an antiviral agent employed as model drugs across the skin of male hairless rats. In all cases, a satisfactory good agreement based on the diffusion with memory has been found. However, the model based on the new definition of fractional derivative gives a better description of the experimental data, on the basis of the residuals analysis. The use of the new definition widens the applicability of the fractional derivative to diffusion processes in highly heterogeneous systems.

1. Introduction

The penetration of drugs through intact skin can be considered as a process of molecular diffusion across a composite multilayer membrane, whose principal barrier to diffusion is localized within the stratum corneum (SC). As a matter of

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fact, skin is a multilayered membrane composed by the stratum corneum that represents the outermost layer and by the epidermis and the dermis, which of them characterized by different structural and physico-chemical properties. While epidermis and dermis exert a barrier towards lipophilic compounds, stratum corneum, consisting of several layers of hydrated and keratinized cells, suspended in an extracellular lipid matrix, acts as a rather impermeable layer to most of drugs and other hydrophilic substances.

This biological system, because of its structural organization, is particularly suitable to be described, as far as the drug permeation is concerned, by a diffusion coefficient able to take into account the intrinsic heterogeneity of the system. This can be conveniently taken into account by a diffusion equation with fractional derivative that, because of its intrinsic nature, is constructed by adding to the initial value the successive weighted increments over time.

We have recently proposed that in highly heterogeneous systems, and particularly in the case of the skin [1], the overall transport process could be described by the second Fick law modified by introducing a memory formalism (diffusion with memory) [2–5]. This approach has been employed to describe the concentration profile inside a biological membrane when a sudden change of the concentration in the medium bathing one of its face is applied.

The diffusion with memory based on a fractional derivative approach has been already successfully used in different fields, ranging from electromagnetism [6] to fractal media [7]. In particular, fractional derivatives have been employed to model the rheological properties of solids [8], in the constitutive equations of polarizable media in the time domain [6] and in chaotic systems [9] and, more recently, in the dynamics of glass-forming materials [10] and in demography and economy [11,12].

In this note, we apply the diffusion with memory formalism to the penetration of low molecular weight solutes through a composite membrane modeled as a bilayer structure consisting of a layer of thickness h adjoining a semi-infinite medium, each of them characterized by different diffusion parameters.

The introduction of memory into the classical diffusion equations (Fick's equations) is carried out by introducing, besides the classical Caputo definition of the fractional derivative, a new definition of the fractional derivative recently proposed by Caputo and Fabrizio [13] with a different kernel, removing the singularity present in the classical Caputo fractional derivative.

We compare the model predictions based on these two different definitions with some experimental results of drug penetration into skin *in vitro* we have previously analyzed in the framework of the classical Caputo definition [6]. Moreover, this analysis was extended to other diffusion processes, such as permeation of water across the human skin and the diffusion of an antiviral agent through the skin of male rats. While both the diffusion models are able to give a satisfactory agreement with the experimental data, the model based on the new definition of fractional derivative proposed by Caputo and Fabrizio [13], on the basis of the simple residual analysis furnishes a little bit better agreement.

2. Definition of fractional derivatives

The usual Caputo fractional derivative of order u is defined as [14,15]

$$D_t^u f(x,t) = \frac{1}{\Gamma(1-u)} \int_0^t \frac{1}{(t-\tau)^u} \left[\frac{\partial f(x,t)}{\partial t}\right]_{t=\tau} \mathrm{d}\tau \tag{1}$$

with $0 < u < 1$ and $\Gamma(x)$ the Euler Gamma function. It is worth noting how the memory function captures the past. What the fractional derivative memory functions is remembering is the past values of the function, which implies that the function is constructed by adding to the initial value the successive weighted increments over time. The increments per unit time are represented by the first order derivative under the integral sign and the weights are represented by the factor of the first order derivative in Eq. (1) which are decreasing with increasing time separation from the time t. Thus, a variable's value is a weighted mean of its past values.

Recently, Caputo and Fabrizio [13] have proposed a new definition of the fractional derivative according to the expression

$$D_t^u f(x,t) = \frac{1}{1-u} \int_0^t \exp\left[-\frac{u(t-\tau)}{1-u}\right] \left[\frac{\partial f(x,t)}{\partial t}\right]_{t=\tau} \mathrm{d}\tau \tag{2}$$

whose kernel, contrarily to what happens in the usual Caputo fractional derivative (Eq. (1)), does not have a singularity for $t = \tau$.

For both the fractional derivatives (Eqs. (1) and (2)), it is possible to evaluate the Laplace Transform (LT), which, in the variable s, gives

$$LT[D_t^u f(x,t)] = \frac{1}{\Gamma(1-u)} \int_0^\infty \exp(-st) \int_0^t \frac{1}{(t-\tau)^u} \left[\frac{\partial f(x,t)}{\partial t}\right]_{t=\tau} \mathrm{d}\tau \mathrm{d}t = s^u LT[f(x,t)] - f(x,0) s^{u-1} \tag{3}$$

in the case of the usual Caputo derivative (Eq. (1)) and

$$LT[D_t^u f(x,t)] = \frac{1}{1-u} \int_0^\infty \exp(-st) \int_0^t \left[\frac{\partial f(x,t)}{\partial t}\right]_{t=\tau} \exp\left[\frac{u(t-\tau)}{1-u}\right] \mathrm{d}\tau \mathrm{d}t = \frac{sLT[f(x,t)] - f(x,0)}{s + u(1-s)} \tag{4}$$

in the case of the new definition (Eq. (2)).

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