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Impact of anomalous transport kinetics on the progress of wound healing

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ABSTRACT

This work focuses on the transport kinetics of chemical and cellular species during wound healing. Anomalous transport kinetics, coupling sub- and superdiffusion with chemotaxis, and fractional viscoelasticity of soft tissues are analyzed from a modeling point of view. The paper presents a generalization of well stablished mechano-chemical models of wound contraction (Murphy et al., 2012; Valero et al., 2014) to include the previously mentioned anomalous effects by means of partial differential equations of fractional order. Results show the effect that anomalous dynamics have on the contraction rate and extension and on the distribution of biological species, and indicators of fibroproliferative disorders are identified.

1. Introduction

Wound healing is a complex and highly intricate phenomenon that evolves over three major phases (inflammation, proliferation and remodeling) that overlap on time [3]. A key aspect on the timely development of these phases rests on the mobilization (i.e. migration and/or diffusion) and the communication of appropriate cellular and biochemical species, coupled with the mechanical status of the affected tissue. In this process, cells play a crucial role acting as sensors and transducers of the mechanical and biochemical signals [4]. A successful path to complete and fully functional healing of the wound is obtained only when biological signals are sent and interpreted on due time, starting with the coagulation cascade and finalizing with the remodeling of the scar tissue.

The causes behind an impaired healing are frequently related to local hypoxia, infection (or prolonged inflammatory response) and altered cellular response to stress [5]. These pathologies are frequent in diabetic ulcers and pressure ulcers. Diabetes prolongs the inflammatory response and degrades the granulation tissue, delaying the reepithelialization of the wound and the recovery of its tensile strength [4]. Diabetes also hinders vascular ingrowth, affecting directly to the oxygenation of the surrounding tissue, necessary to sustain cellular function. Tissue hypoxia and subsequent necrosis are characteristic features of pressure ulcers, that appear on load bearing regions on patients with reduced or impeded mobility [6].

Conventionally, wound healing has been investigated from an experimental perspective, mainly focused on *in vitro* models of cell migration and cell force estimation [7]. Although more scarcely, animal models have also been developed to investigate wound closure [8–10]. This work, however, looks at the development of *in silico* models to study the course of wound healing. Traditionally, mathematical models have been developed from a continuous and macroscopic perspective giving rise to systems of diffusion-convection-reaction equations that couple the interactions between different types of cellular species, growth factors and the tissue deformation. The interested reader is referred to [11], and references therein, to find an extensive review of the state of the art in wound healing models.

The above-mentioned models rest on a macroscopic approximation of transport kinetics based on a Gaussian distribution of particle jumps. This gives raise to homogeneous diffusion terms and homogeneous diffusion–reaction systems. These type of equations capture qualitatively the formation of patterns, and allow to correlate these patterns to physically measurable parameters. An example of this is the development of traveling waves in nonlinear reaction–diffusion equations. However, anomalous transport kinetics are frequent on biological processes. These kinetics present a mean square displacement proportional to a power of time, $\langle \Delta x(t)^2 \rangle \propto t^{\alpha}$, where the power α differs from 1. When $\alpha < 1$, the transport is referred as subdiffusive, while when $\alpha > 1$ it is known as superdiffusive. Subdiffusion is characteristic in materials of an hierarchical structure, where the diffusing particles may

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get trapped during transport. It has been reported in porous media [12] and in the transport of molecules at the cellular level [13–15]. On the other hand, superdiffusion presents random walks with an enhanced travel distance, known as Lévy flights. In biology, Lévy flights have been used to analyze the evolution of epidemics [16,17]. An excellent review of modeling aspects and fields of application of sub- and superdiffusion processes can be found [18]. The formulation of these phenomena from a homogenized and continuous perspective is achieved by means of partial differential equations of fractional order [19]. However, to the author's knowledge, anomalous diffusion has not been applied yet to study (pathological) wound healing despite its great potential to explain altered transport kinetics.

Hence, this work revisits a well established contraction and closure model [1,2] to incorporate anomalous transport kinetics. Fractional order kinetics will be incorporated for the evolution of a mitotic and chemotactic growth factor (which takes into account the combined effects of PDGF and TFG-β), the density of fibroblasts and the deformation of the tissue. Thus, a physically based system of fractional partial differential equations that includes sub- and superdiffusion from a continuum perspective will be presented. The constructed fractional order model will be used to infer the impact of anomalous transport kinetics on the progress of healing.

2. Fractional order partial differential equations

In order to introduce the nomenclature and formulation of the governing equations, the basic definitions of the fractional order differential and integral operators will be given first. In that context, the Riemann–Liouville and Caputo definitions are considered. In the presentation, the notation used by Mainardi [20] will be used without loss of generality.

The Riemann–Liouville (RL henceforth) definition of a fractional order integral operator or order α ($\alpha > 0$ in this notation) of a scalar function $f(t)$ fulfilling $f(t) = 0$ for all $t < 0$ is given by

$$ {}^{RL}_{0}\mathbf{I}^{\alpha}_{t} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau)\, d\tau, \tag{1} $$

where $\mathbf{I}$ is introduced to denote the integral operator and Γ denotes the Gamma function. The Riemann-Liouville fractional order differential operator acting of f is defined as the mth order derivative of the $(m-\alpha)$th order integral of f, that is,

$$ {}^{RL}_{0}\mathbf{D}^{\alpha}_{t} f(t) = \frac{d^m}{dt^m}\left({}^{RL}_{0}\mathbf{I}^{m-\alpha}_{t} f(t)\right), \tag{2} $$

where m is the smallest natural number above α (that is $m-1 \leq \alpha < m$, $m \in \mathbb{N}$). This result in the usual definition of the fractional order derivative

$$ {}^{RL}_{0}\mathbf{D}^{\alpha}_{t} f(t) = \frac{1}{\Gamma(m-\alpha)} \frac{d^m}{dt^m} \int_0^t (t-\tau)^{m-\alpha-1} f(\tau)\, d\tau, \tag{3} $$

where $\mathbf{D}$ has been introduced to denote the fractional order differential operator. These definitions (Eqs. (1) and (3)) extrapolate the natural order integral and differential operators, that is, they coincide with the nth order integral and derivative of function f when $\alpha = n$.

An alternative definition of the fractional order derivative is due to Caputo (C henceforth), which interchanges the order of the integral and differential operators in the Riemann–Liouville definition

$$ {}^{C}_{0}\mathbf{D}^{\alpha}_{t} f(t) = {}^{RL}_{0}\mathbf{I}^{m-\alpha}_{t}\left(\frac{d^m f(t)}{dt^m} \right), \tag{4} $$

where again m is the smallest natural number above α. This change effectively results in the definition

$$ {}^{C}_{0}\mathbf{D}^{\alpha}_{t} f(t) = \frac{1}{\Gamma(m-\alpha)} \int_0^t (t-\tau)^{m-\alpha-1} \frac{d^m f}{dt^m}(\tau)\, d\tau. \tag{5} $$

This definition of the derivative operator coincides with the natural order derivative only when the order α approaches m (from the left). For values of α approaching to $m-1$ (from the right) the following relation holds [21]

$$ \lim_{\alpha \to (m-1)^+} {}^{C}_{0}\mathbf{D}^{\alpha}_{t} f(t) = \frac{d^{m-1} f}{dx^{m-1}}(t) - \frac{d^{m-1} f}{dx^{m-1}}(0^+). \tag{6} $$

Thus, the Caputo derivative extrapolates the classical derivative only for functions with all its derivatives vanishing at the origin. This subtle constrain connects with the relation between the Riemann–Liouville and Caputo differential operators [20], which is

$$ {}^{C}_{0}\mathbf{D}^{\alpha}_{t} f(t) = {}^{RL}_{0}\mathbf{D}^{\alpha}_{t} f(t) - \sum_{k=0}^{m-1} \frac{d^k f}{dt^k}(0^+) \frac{t^{k-\alpha}}{\Gamma(k-\alpha+1)}. \tag{7} $$

A consequence of Eq. (7) is that the Riemann–Liouville and Caputo derivatives coincide on all functions f with vanishing derivatives at origin.

Another important subject on the formulation of fractional order differential equations is proper definition of the initial conditions (or boundary conditions in a general context). The Caputo formulation allows for the use of natural order derivatives, which connects directly with physical interpretation of the problem. However, the Riemann–Liouville formulation requires the use of fractional order initial conditions, of the type

$$ \lim_{t \to 0+} {}^{RL}_{0}\mathbf{D}^{\alpha-k}_{t} f(t) = f_k \tag{8} $$

for $1 \leq k \leq m$, which gives raise to both fractional order integrals and derivatives evaluated at the origin. These type of initial (or boundary) conditions result in practice more difficult to connect to the physical background. In that respect, Heymans and Podlubny [22] analyze the physical interpretation of these conditions in the framework of fractional viscoelasticity for certain load regimes, and Podlubny [23] provide a general discussion of these conditions. However, many authors have chosen to deal with homogeneous initial (and boundary) conditions [24–26] or directly formulate the problem in terms of the Caputo derivative [21,27] in order to overcome this issue.

2.1. Fractional order diffusion equations

In the field of biology, anomalies in the diffusion pattern have been reported for molecular transport at the cellular level (on the cell membrane [28] and on the cytoplasm [29]) and at the tissue level (water molecules on rats brain [30] and electric fronts in cardiac muscles [31]). Anomalous migration of fibroblasts has also been observed on *in vitro* assays [32] relating the migration kinetics with cytoskeletal disruption during anti-cancer drug treatment. The physical justification for these observations rests on the structural heterogeneity of the transport medium. This heterogeneity may cause that macromolecules get temporally trapped, effectively delaying the diffusion front, or that molecules travel arbitrarily large distances, effectively accelerating the diffusion front.

A macroscopic approximation of the above described transport kinetics is obtained through the formulation of a fractional order diffusion equation for the diffusing species. The fractional order differential operator can be introduced in the temporal variable (giving raise to subdiffusion) or in the spatial variable (giving raise to superdiffusion). In general, when the fractional differential operators act on both the temporal and spatial variables, the so-called anomalous diffusion pattern is obtained. For the remaining of the section, the variable $c = c(x,t)$ will denote the concentration at location x and at time t of a general purpose diffusing specie.