Simplifying biochemical tumorous bone remodeling models through variable order derivatives

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ABSTRACT

Bone is a living tissue that is constantly being renewed, where different cell types can induce a remodeling action to its structure. These mechanisms are typically represented through differential equations, accounting for the biochemical coupling between osteoclastic and osteoblastic cells. Remodeling models have also been extended to include the effects of tumorous disruptive pathologies in the bone dynamics.

This article provides a novel approach to existing biochemical models, acting on two different stages. First, the models are said to physiologically better explain an osteolytic metastatic disease to the bone than the multiple myeloma previously considered. Second, and most importantly, variable order derivatives were introduced, for the first time in biochemical bone remodeling models. This resulted in a set of equations with less parameters that describe tumorous remodeling, and provide similar results to those of the original formulation. A more compact model, that promptly highlights tumorous bone interactions, is then achieved. Comparison of simulations and parameters is provided.

Such results are a one-step-closer insight to, in a near future, easily provide clinical decision systems ensuring tailored personalized therapy schemes, for more efficient and targeted therapies.

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1. Introduction

Contrary to what one may consider intuitive, bone is not made of static tissue as it undergoes spatially heterogeneous and asynchronous remodeling cycles [1]. Such is due to the activity of bone constituent cells: osteoclasts, responsible for bone resorption, and osteoblasts, that are bounded to form bone [2]. In this tightly coupled mechanism between bone cells, resorption is consistently followed by a formation phase in a site-specific manner, which allows to consider that osteoclasts also regulate the activity of osteoblasts [3].

This fine tune balance is disrupted in the presence of a tumor, changing it for benefit of the disease. Studying such behavior is important both because of primary tumors in the bone, and also because of metastatic cases due to other types of cancer. In particular, breast and prostate cancer are prone to such development [4]. For tumor-induced lesions of osteolytic nature, promotion of osteoclast activity and change in the number/activity of osteoblasts occurs in a process not fully understood [5,6].

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The biochemical process of bone remodeling can be replicated through mathematical and computational models, allowing for a comparison between healthy bone behavior with pathological states [7,8]. They consist of a system of ordinary differential equations that relate the interactions between osteoclasts and osteoblasts, by reproducing the effects of autocrine and paracrine control mechanisms. The resulting calculation of the dynamic response of these cell populations determines the changes in bone mass in the bone remodeling cycles. A local model, for healthy bone tissue, was initially proposed in [7] and further extended in [8] to include the tumorous influence of multiple myeloma (MM) disease and a non-local approach with diffusion.

Biological processes often present phenomena such as anomalous diffusion or viscoelasticity [9,10], which can be modeled using fractional derivatives. Consequently, existing models can be improved by including a fractional order [11,12]. In this way, several biological tissues have been adequately described (e.g. the human respiratory system [13], the circulation of sap in leaves [14]). It is possible, even though not trivial, to present a geometrical or a physical interpretation of the resulting differential equations [15]. In the case under concern, bone remodeling is expected to present anomalous diffusion. However, many physical processes appear to exhibit a fractional order behavior that varies with time or space [16,17].

Here, the referred models are said to better explain an osteolytic metastatic bone environment, instead of MM. Type-$\mathcal{D}$ variable order derivative construction was introduced, for the first time in bone remodeling, allowing the tumor's disruptive action to be explained in more succinct and straightforward equations. Such provided similar results with more compact models than those being currently used.

Previously published models are given in Section 2, followed by a summary of variable order derivatives definitions in Section 3. The new local and non-local models developed are given in Section 4, where discussion for the provided simulations can be found in Section 5. Future work and conclusions are summed up in Section 6.

In all that follows, D^1 is the first order derivative in order to time ($\frac{d}{dt}$). Variable order is given by $\alpha(t)$ or $\alpha(t, x)$, and $D^{\alpha(t)}$ or $D^{\alpha(t,x)}$ represent the time variable order derivatives of an order time or time and space dependent, respectively. All models here presented use dimensionless variables and parameters, including the cell populations (see Table 1).

2. Existing models for tumorous bone remodeling

This section presents the published models for healthy and tumorous bone remodeling that were the starting point for this paper. It is divided into local (Section 2.1) and non-local (Section 2.2) constructions.

2.1. Local approach

In the healthy model proposed in [7] and described by Eqs. (2.1), bone remodeling takes the form of an S-system [18]. Coupling the behavior of osteoclasts, $C(t)$, and osteoblasts, $B(t)$, is done through biochemical autocrine (g_{CC}, g_{BB}) and paracrine (g_{BC}, g_{CB}) factors expressed in the system's exponents. Bone mass density, $z(t)$, is determined through the extent which values of $C(t)$ and $B(t)$ populations exceed their nontrivial steady state, C_{SS} and B_{SS}, respectively. Below such values the populations of osteoclasts and osteoblasts are assumed to consist of less differentiated cells that are unable to resorb or build bone, but are able to participate in autocrine and paracrine signaling. The constants κ_C and κ_B represent the bone resorption and formation activity, respectively. Finally, α_C and α_B are activation rates, and β_C and β_B are apoptosis (programmed cell death) rates.

$$D^1 C(t) = \alpha_C C(t)^{g_{CC}} B(t)^{g_{BC}} - \beta_C C(t) \tag{2.1a}$$

$$D^1 B(t) = \alpha_B C(t)^{g_{CB}} B(t)^{g_{BB}} - \beta_B B(t) \tag{2.1b}$$

$$D^1 z(t) = -\kappa_C \max[0, C(t) - C_{ss}] + \kappa_B \max[0, B(t) - B_{ss}]. \tag{2.1c}$$

The tumor burden in the healthy bone remodeling environment, as proposed in [8] and presented in Eqs. (2.2) for MM bone disease, acts through the autocrine and paracrine regulations pathways in the form of r_{ij} parameters. New variable $T(t)$ represents the tumor cells density at time t, with a Gompertz form of constant growth $\gamma_T > 0$. Tumorous action is considered independent of bone loss and translates a possible maximum tumor size of L_T. The bone mass equation is the same as that of Eq. (2.1c).

In Fig. 1, simulation of both healthy and tumorous bone can be found, presenting the evolution of the osteoclasts and osteoblasts populations and bone mass.

$$D^1 C(t) = \alpha_C C(t)^{g_{CC}\left(1 + r_{CC}\frac{T(t)}{L_T}\right)} B(t)^{g_{BC}\left(1 + r_{BC}\frac{T(t)}{L_T}\right)} - \beta_C C(t) \tag{2.2a}$$

$$D^1 B(t) = \alpha_B C(t)^{\left(\frac{g_{CB}}{1 + r_{CB}\frac{T(t)}{L_T}}\right)} B(t)^{\left(g_{BB} - r_{BB}\frac{T(t)}{L_T}\right)} - \beta_B B(t) \tag{2.2b}$$

$$D^1 T(t) = \gamma_T T(t) \log\left(\frac{L_T}{T(t)}\right). \tag{2.2c}$$