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Bone remodeling as a spatial evolutionary game

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ABSTRACT

Bone remodeling is a complex process involving cell–cell interactions, biochemical signaling and mechanical stimuli. Early models of the biological aspects of remodeling were non-spatial and focused on the local dynamics at a fixed location in the bone. Several spatial extensions of these models have been proposed, but they generally suffer from two limitations: first, they are not amenable to analysis and are computationally expensive, and second, they neglect the role played by bone-embedded osteocytes. To address these issues, we developed a novel model of spatial remodeling based on the principles of evolutionary game theory. The analytically tractable framework describes the spatial interactions between zones of bone resorption, bone formation and quiescent bone, and explicitly accounts for regulation of remodeling by bone-embedded, mechanotransducing osteocytes. Using tools from the theory of interacting particle systems we systematically classified the different dynamic regimes of the spatial model and identified regions of parameter space that allow for global coexistence of resorption, formation and quiescence, as observed in physiological remodeling. In coexistence scenarios, three-dimensional simulations revealed the emergence of sponge-like bone clusters. Comparison between spatial and non-spatial dynamics revealed substantial differences and suggested a stabilizing role of space. Our findings emphasize the importance of accounting for spatial structure and bone-embedded osteocytes when modeling the process of bone remodeling. Thanks to the lattice-based framework, the proposed model can easily be coupled to a mechanical model of bone loading.

1. Introduction

Bone remodeling is a complex mechano-biological process that is critical for maintenance of the healthy skeleton (Robling et al., 2006). During bone remodeling, bone-resorbing osteoclasts remove old and damaged bone while bone-matrix producing osteoblasts generate new bone tissue to restore structural integrity, see Fig. 1A. The recruitment of osteoclasts, and subsequently osteoblasts, is mediated by bone-embedded, mechano-sensing osteocytes, which translate load-induced mechanical strains into signals to control the adaptive remodeling process (Raggatt and Partridge, 2010). Disruption of the interactions between the key cellular components of remodeling can lead to pathological states. Such is the case in osteoporosis, where hormonal changes during menopause cause imbalances in the remodeling process and can lead to fracture-prone bones, and in Paget's disease, a condition where bone undergoes cycles of uncontrolled resorption and formation (Feng and McDonald, 2011).

Over the past decade, there has been a surge in quantitative modeling of the cellular processes and signaling pathways that regulate bone remodeling. The first such models, developed by Lemaire et al. (2004), Komarova et al. (2003), Komarova (2005), and colleagues, focused on the temporal dynamics of remodeling at a fixed location in the bone. Based on systems of ordinary differential equations (ODEs), these models successfully described the interactions between osteoclasts and osteoblasts and the resulting bone mass balance. The original ODE models have since been applied and extended by various authors, see e.g. the work by Pivonka et al. (2008), Buenzli et al. (2012), Ji et al. (2012), and colleagues. For further references, as well as an overview of modeling studies with focus on the mechanical aspects of remodeling, we refer to the review articles (Pivonka and Komarova, 2010; Webster and Müller, 2011).

While ODE models provide valuable insights into the complex dynamics of physiological and pathological bone turnover, they are not able to capture salient spatial features of the remodeling process (Parfitt, 1994). In fact, the latter takes place on the complex geometries of cortical and trabecular bone, and paracrine signaling between bone cells, which is mediated by soluble chemokines, allows for non-local regulation (Khosla, 2001). To model such non-local phenomena, our group (Ryser et al., 2008, 2010, 2012) and others (Buenzli et al., 2011; Graham et al., 2012) previously developed partial differential equation

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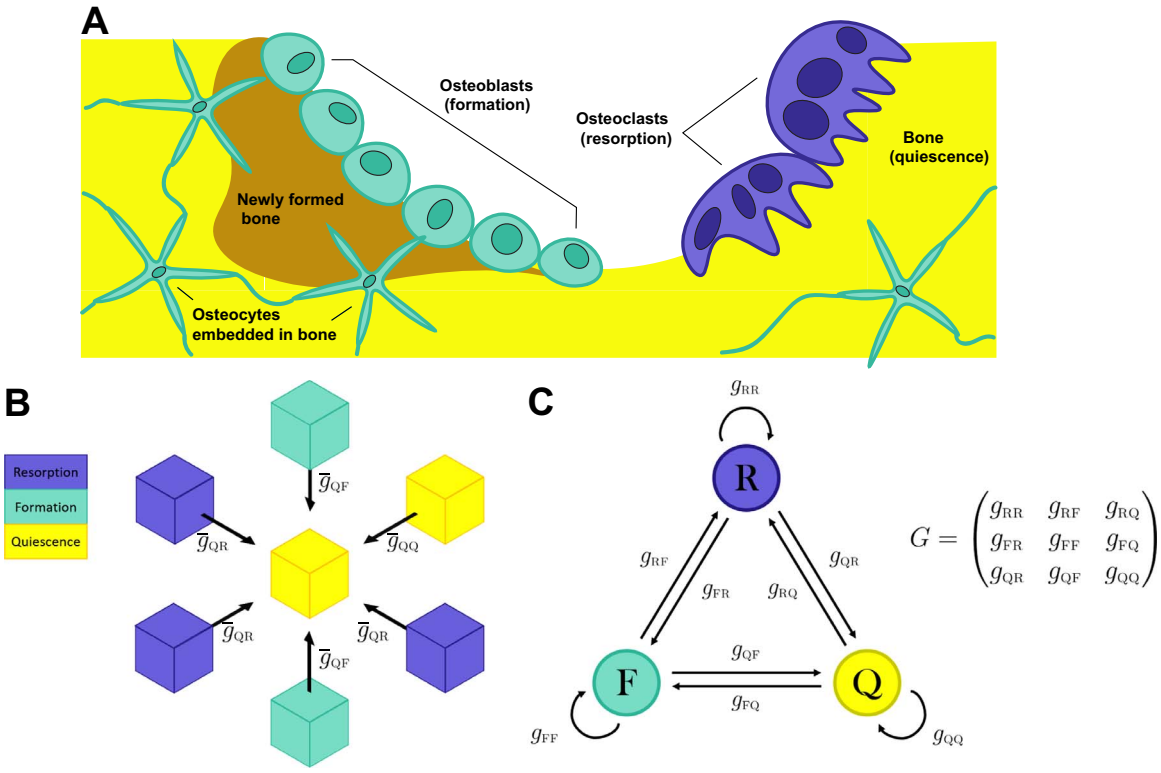

Fig. 1. *Bone Remodeling as a Spatial Evolutionary Game.* (A) Bone remodeling is a complex multicellular process necessary for maintenance and adaptation of a healthy skeleton. Bone resorbing osteoclasts (purple) remove old and damaged bone (yellow), and osteoblasts (green, round) produce new bone matrix. Once osteoblasts have completed their task of producing new bone, they either die or become embedded in the bone tissue where they differentiate into osteocytes (green, star-shaped). Osteocytes are connected through a complex network and are thought to play an integral role in sensing bio-mechanical stimuli and translating them into chemical signals to orchestrate the remodeling process by osteoclasts and osteoblasts. (B). In the spatial setting, the expansion rate of a zone (center) is determined by the constitution of its neighbors and the corresponding interaction strengths $\overline{g}_{XY}$. Note that $\overline{g}_{XY}$ quantifies the expansion rate contribution of a zone of type Y to a zone of type X. The contributions are additive, see Eq. (1). (C) The pay-off matrix $G = (g_{ij})$ of the non-spatial evolutionary game specifies the interaction network between resorption (R), formation (F) and quiescence (Q). Note that the expansion rate and payoff matrices are related by $\overline{G} = \mathbf{1} + \omega G$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

(PDE) models of bone remodeling. In addition, discrete agent-based models of the spatial remodeling dynamics were introduced to study the dynamics of individual remodeling units (Buenzli et al., 2012; van Oers et al., 2008, 2011). Spatial aspects of the remodeling biology are also captured in various biomechanical models of bone adaptation (Badilatti et al., 2016; Cox et al., 2011; Scheiner et al., 2013).

These spatial extensions of the original ODE models are endowed with high-dimensional parameter spaces and their analyses rely on computer simulations. In consequence, to gain mechanistic insights and understand which model components are relevant to regulate and maintain physiological remodeling, systematic and extensive parameter space explorations are necessary, and a complete characterization of the dynamic regimes is generally beyond reach. Furthermore, most spatial models focus on osteoclast and osteoblast dynamics only, while treating bone as a passive constituent that is either resorbed and deposited by the two active players of the process. Based on experimental evidence (Nakashima et al., 2011; Xiong et al., 2011) however, it has become clear that quiescent bone and embedded, mechano-transducing osteocytes play a key role in the regulation of remodeling.

In view of the above limitations of current spatial models, our objective was to develop a spatial model of bone remodeling biology that (i) is amenable to analysis and complete classification in the sense of the original, reductionist ODE model by Komarova and colleagues (Komarova et al., 2003) and (ii) treats quiescent bone and embedded osteocytes as an active part of the remodeling dynamics. We focused on trabecular remodeling and developed our model in the framework of evolutionary game theory (EGT). The latter was introduced by Maynard Smith in 1982 (Smith, 1982), and has since been used to study a wide range of systems in biology and ecology (Frey, 2010; Hammerstein and Selten, 1994; Nowak, 2006; Broom and Rychtar, 2013). The analysis of spatial EGT models poses substantial technical difficulties and is a field of active research. Recent advances by Cox et al. (2013) and Durrett (2014) on the weak selection limit for EGTs enabled the analyses in this article.

2. Methods

2.1. Spatial model

We start by introducing the general idea, and then proceed to construct the formal process. To model physiological remodeling of trabecular bone (Fig. 1A) in a discrete spatial setting, we partition the volume of trabecular bone into zones of bone resorption, bone formation and quiescent bone. Zones of resorption are populated by bone matrix degrading osteoclasts, and zones of formation are populated by osteoid producing osteoblasts. Quiescent zones on the other hand consist of bone matrix and embedded osteocytes. We then allow the different zones to interact in a probabilistic manner, resulting in growing and shrinking patches of resorption, formation and quiescence. For example, if a zone of formation (osteoblasts) is adjacent to a zone of quiescence (bone), then the zone of formation is expected to convert to a zone of quiescence, consisting of newly formed bone with embedded osteocytes. Conversely, if a zone of quiescence (bone) is adjacent to a zone of resorption (osteoclasts), the former is expected to vanish and be replaced by the expanding zone of resorption. The resulting process is an evolutionary competition between neighboring zones. Due to the complex interactions between cell types, the probability of each zone to invade or to be invaded depends on the