Forced Lotka-Volterra System for Bone Mechanobiology

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Summary. The architecture and quality of bone tissue in an adult organism predominantly depends on bone cellular organisation and communication processes that are highly driven by external mechanical loading. How physical forces and changes in the mechanical properties of cells and tissues contribute to development, cell differentiation, physiology, and disease, in general, is a major interest of mechanobiology. This paper outlines how mathematical models can help to improve current understanding of bone cellular mechanobiology. Here we introduce an adapted mathematical model for bone remodeling in the form of generalized S-system equations (Lotka-Volterra system) of fifth order that includes periodic received and transduced signal of external loading. Critically, we approach the modelling through both deterministic and stochastic methods, which allow us to consider the intrinsic noisiness of the process.In particular, this model includes osteocytes mechanobiology, which, apart from their biochemical processes and their interactions with other bone remodeling cells, includes external periodic signal transduction and influence that represents a significant advance to the field.

Background and Aims

The bone cell lineages are permanently active in the process of bone remodelling that resorbs old and forms the new content of bone. These activities happen on the daily base with a progression of several micrometres of local bone turnover. The bone architecture and quality depend on many biological, biochemicals, hormonal and physical factors among which external static and dynamic loading play an important role. The bone adaptive mechanobiological processes are governed by the osteoblasts (OBs), osteoclasts (OCs), and osteocytes (OcYs) cells working in concert, all capable of transducing mechanical strain signals into biochemical cues for osteogenesis [1]. However, Osteocytes (OcYs) in particular have been shown in vitro to be the most mechanosensitive bone cell type, demonstrating a higher intrinsic sensitivity to loading than other osteogenic cells. They have also recently been shown to direct osteogenesis in other bone cell types, reinforcing the theory that osteocytes sense mechanical loading in the bone matrix and then orchestrate the adaptive bone remodeling response [2]. Owing to their presence deep within bone matrix, direct experimental observation of osteocytes in vivo has proven extremely challenging. As such, the precise mechanical stimuli, which they experience in vivo, and the mechanisms whereby they sense and transmit these stimuli, remain unknown. Although it is possible to mechanically stimulate bone and quantify the tissue-level changes that occur, it is still extremely challenging to simultaneously delineate the cellular and molecular mechanisms that give rise to these changes. Further, the complexity of the skeletal processes and their interactions with the rest of the body limits the ability of a single biological model to capture all of the relevant biological, biochemical, and biophysical mechanisms of remodelling on all scales simultaneously. Moreover, the parameterization of an established accompanying mathematical model is difficult, given its dependency on the accuracy and availability of data. However, in-silico experiments on established mathematical model reveal important features of nonlinear connections between variables and dependency on parameters of the system. In many cases, the quality of a scientific field depends on how well the mathematical models, developed on the theoretical side, agree with the results of repeatable experiments. Lack of agreement between theoretical mathematical models and experimental measurements often leads to important advances as better theories are developed. With this research, we wish to emphasize the importance, reliability and credibility of mathematical models as a great way of cementing biological intuition. Specifically, they provide causative mechanisms linking inputs and outputs, thereby illuminating underlying assumptions that determine a biological system's dynamics. Finally, they offer a means of predicting new outcomes, as well as highlighting the most sensitive modelled components, resulting in the construction of new experimental hypotheses and more focused experimentation.

Methods and mathematical models

To address the question of how different bone cells interact with each other and the bone microenvironment during remodelling, several cell population models have been proposed in Refs. [3-6]. These types of models are able to monitor changes in cell numbers and bone volume over time and they all modelled the free dynamics of the bone cell system. The formalism of a cell population model can be generalised to be of the form of a S-System of equations of n^{th} order that corresponds to the number of included cellular lineages,

$$\frac{du_i}{dx} = \alpha_i \prod_{j=1}^{2} u_j^{g_{ij}} - \beta_i u_i, i = 1, 2, \dots, n. \qquad (1)$$

If we include OcY, OB, OC and preosteoblastic (pOB) lineages of cells together with a bone mass equation it will be system of 5^{th} order ($n = 5$). System (1) is a homogeneous system of coupled ordinary nonlinear differential equations that is more specifically. In one cycle of targeted remodeling the number of activator cells, both resorbing and forming, is bounded above by approximately 10 OCs and up to 300 OBs, so that in the dynamics of the system (1) the number of OCs drops below one, which occurs frequently. Of course, since we are dealing with exact numbers of cells, such a measurement is unrealistic.

Critically, the problem stems from the direct use of differential equations that assume a modelled population is large enough, for a continuum hypothesis to approximately hold. This hypothesis is obviously invalid at such small population sizes. Thus, for such low numbers of cells it is more correct to produce a discrete interaction model. Specifically, we use a stochastic analogue to simulate the creation and degradation, which encapsulates the noisy features of individual cell division and death [7-9]. From system (1) we are able to extract the stochiometric creation and degradation relations, and present its probabilistic analogue:

$$\emptyset \xrightarrow{\alpha_i u_i u_j} u_i, u_i \xrightarrow{\beta_i} \emptyset, i = 1, 2, \dots, n \text{ and } j \neq i. \qquad (2)$$

Although parameter values exist in the literature they are mainly approximate and are proposed to simplify and justify the model. Further, in all of the literature it is assumed that the γ_{ij} parameters are constant. However, in real bone remodelling processes the γ_{ij} parameters may depend on time and other factors. Unfortunately, these parameters cannot be directly measured and have to be estimated. Based on these recent biological experimental findings we introduce the modification of the model by editing the power low term γ_{31} to time dependent oscillatory function $\gamma_{31}(1 + \sin(\theta t))$, what represent transduced signal of OcY, and inserting the mechanical periodic excitation $A(1 - \cos(\theta t))$ to the responding OcYs.

Results & Discussion

We find that the model can capture the essential autocrine, paracrine and synergistic characteristics of bone cell communication processes in response to the external incentives. Specifically, including oscillatory signals with small delays between received and send a signal by OcY provides the closest matches between mathematical data and biology theory. This can be seen from Fig. 1 where after the period of resorption, the depression of green z line below zero, come the significant changes in the activation of osteoblasts (yellow B line) that results in formation period, the green line above the zero. Comparing with the green line at Fig 1 a) that has no over formation above steady-state value $z_{ss} = 100$. We prove that under the influence of the external periodic signal the local formation of the newly remodelled bone will exceed the amount of resorbed old bone.

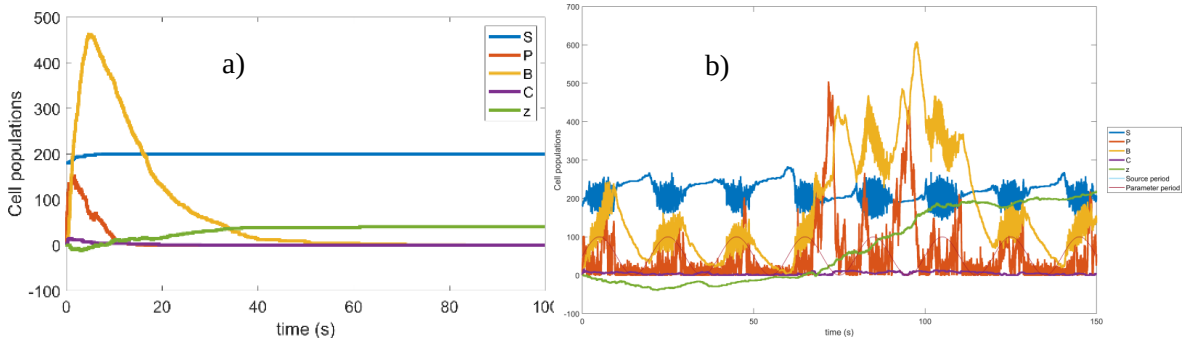

Figure 1: One cycle of bone remodeling: a) free cell communication; b) periodically forced dynamics with external periodic source and parameter γ_{31} out of synchronization by a factor of $\pi/2$, all parameter values are taken from [6] except $k_2 = 0.014$

Conclusions

The results of our research highlighted the importance of the external excitation and mechanotransduction of the signal by the bone cell in the regular bone turnover. The in-silico experiments with forced Lotka-Volterra system of population equations pinpointed the importance of nonlinear deterministic and stochastic analysis in the field of mechanobiology.

References

[1] Giorgi, M., Verbruggen, S. W., & Lacroix, D. (2016). In silico bone mechanobiology: modeling a multifaceted biological system. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, *8*(6), 485–505. https://doi.org/10.1002/wsbm.1356;

[2] Bonewald L. Osteocytes: a proposed multifunctional bone cell. J Musculoskelet Neuronal Interact 2002, 2:239.

[3] Simonovic J., (2019), *Simultaneous multi-parametric analysis of bone cell population model*, NODYCON2019 Proceedings, Editors: Prof. B. Balachandran (University of Maryland), Prof. J. Ma (Lanzhou University of Technology), Prof. J.A.T. Machado (Polytechnic Institute of Porto), Prof. G. Stepan (Budapest University of Technology and Economics), and Prof. W. Lacarbonara (Sapienza University of Rome), Springer Conference, *pp.*----, *ISBN*---- accepted for publishing (Dec. 2019)

[4] Pivonka, P., & Komarova, S. V. (2010). Mathematical modeling in bone biology: From intracellular signaling to tissue mechanics. *Bone*, *47*(2), 181–189. https://doi.org/10.1016/j.bone.2010.04.601

[5] Jerez, S. and Chen, B., (2015). Stability analysis of a Komarova type model for the interactions of osteoblast and osteoclast cells during bone remodeling. Math. Biosci., 264, pp.29-37.

[6] Graham, J. M., Ayati, B. P., Holstein, S. A., & Martin, J. A. (2013). The Role of Osteocytes in Targeted Bone Remodeling: A Mathematical Model. *PLoS ONE*, *8*(5), 10–14. https://doi.org/10.1371/journal.pone.0063884

[7] Van Kampen, Nicolaas Godfried. *Stochastic processes in physics and chemistry*. Vol. 1. Elsevier, 1992.

[8] Gillespie, Daniel T. "Stochastic simulation of chemical kinetics." *Annu. Rev. Phys. Chem.* 58 (2007): 35-55.

[9] Schumacher, L. J., Woolley, T. E., & Baker, R. E. (2013). Noise-induced temporal dynamics in Turing systems. *Physical Review E*, *87*(4), 042719.