Simultaneous multi-parametric analysis of bone cell population model

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Abstract. Using the bone cell population mathematical model of system of coupled ordinary differential equations (ODEs) with power law nonlinearities it is possible to properly interpret and analyse bone cell communication dynamics. The system of bone cellular communication is complex and not yet properly described and revealed. The structural analysis has been used here for stability analyses of the problem, as like as for analyses of system sensibility to small parameters changes. The usage of multi-parametric synchronous analysis presented in this paper is the advantage of Mathematica ODE solver that provides functional interpretation of important parameters of dynamics. The models explored in numerous numerical (in-silico) experiments also provide the more realistic approaches to interpreting the development of interventions for patients with bone trauma and diseases, but also for those who want to prioritize the healthy and strong skeleton. This research is a very practical and clear example of nonlinear theory application for bone cell signalling processes modelling and interpretation.

Key words: Bone cell population model, cell signalling, periodic external excitation, nonlinear multi-parametric simulations.

Introduction

Mathematical modelling can be developed to characterize complex bone phenomena, from intercellular signalling to cell division, proliferation, migration and even mutation; from bone remodelling to healing, from tumor growth to cancer metastasis, from osteoarthritis to osteoporosis treatment. Mathematical interpretation and models of this system become even more complex as the higher resolution screening discovers the new players involved in the process, what puts demands on theories, methods and assumptions used and the efficiency of numerical methods employed for solving as well as managing of parameters and data. Mathematical modelling is the tool for synthesis - the process of combining separate elements in order to form a coherent whole –the tool of inductive reasoning, allowing reconstruction of the function of bone as an organ based on the acquired knowledge of elementary processes. The complexity of bone models depends not only on the number of parameters describing different biochemistry and multi-physics influences but also on different time scales and rate of periodicity of processes involved. The most unresolved issues remain linked with ambiguities of mathematical results from in-silico experiments and their discrepancy with in-vivo/vitro experimental results in the modelling of bone tissue. The future advancement of bone biology research will strongly rely on how well experimental and theoretical groups are able to communicate and collaborate with each other. A unique bridge between biological models and experimental validation is more realistic mathematical model together with possibility of numerous in-silico experiments that are an integral part of this paper.

Mathematical model

The system of bone cellular communication, which involves at least three main cellular lineages: forming-osteoblasts (OBs), resorbing-osteoclasts (OCs) and orchestrating-osteocytes (OCYs) cells lineage, with their self (autocrine signalling) and mutual (paracrine signalling) interactions and their interactions with the environment, is complex and elucidate a number of parameters that detail the psychological mechanism of bone tissue adaptation processes. The following are the general form of models developed by several authors [1-4] representing the power of analytical approaches:

$$\frac{du_i}{dt} = \alpha_i f_i(u_i) + k \cdot f_i(u_i, \mu(t)) - \beta_i u_i,\ i = 1,2,3 \quad \text{and}$$

$$\frac{dz}{dt} = -k_1 v_1 + k_2 v_2 \quad \text{for} \quad v_j = \begin{Bmatrix} u_j - \overline{u}_j, & if\ u_j > \overline{u}_j \\ 0, & if\ u_j \le \overline{u}_j \end{Bmatrix},\ j = 1,2 \tag{1}$$

where u_i are the densities of OCs, OBs and OCYs for $i = 1,2,3$, respectively, and $f_i(u_i)$ are the functions giving the growth rates which include the interaction between cell populations by the regulators RANK, RANKL, OPG, TGFβ in the form of power law approximation: $f_1(u_1,u_2) = u_1^{\gamma_{11}} u_2^{\gamma_{21}}$ and $f_2(u_1,u_2) = u_1^{\gamma_{12}} u_2^{\gamma_{22}}$,where $\gamma_{ij}\ for\, i, j = 1,2$ are defined by their autocrine and paracrine regulation. The last, so called bone mass equation describes the activity of bone resorption and formation where z is total bone mass, k_i represents the normalized activities of bone resorption and formation, $\overline{u}_i$ represents the steady states for the OCs and OBs and k is a positive proportionality constant measured in cells day^{-1}. The term $\mu(t)$ functions as a regulator of the bone-remodelling process and includes external signalling, for example, for osteocyte activity via the PHT which is an anabolic agent that stimulates the production of OC. This input function $\mu(t)$ can model RANKL production from osteocytes as well as its regulation by the sclerostin inhibitor [3]. An explicit functional form for $\mu(t)$ linked to osteocytes activity is still to be established and in this paper is proposed as simple periodic function.

In-silico experiment and discussion

The visualization of different system dynamics obtained by small changes of only one parameter (effectiveness of osteoclast autocrine signalling γ_{11}) are presented at Figure1. γ_{11} has been changed from the value of 1.1, Fig1.a) where the solutions exhibit limit cycle, also presented at [4], to the value 1.098, Fig.1b) where yielding damped oscillations converging to the nontrivial steady states $\bar{u}_i$ is presented. It is possible to perform the changes of any parameter and even of all of them simultaneously with this procedure what is a very functional way of parameter`s ranges interpretation and explanation. By performing similar simulations with all involved parameters it is straightforward to decide which of the parameter is the most influencing and most responsible for changes of model dynamics, even if the number of parameters or equations in the model being added. Obtained conclusions and discussions for parameter values and ranges are very applicable for the justification of effectiveness of mathematical models and their compliance with in-vivo experiments of bone cells.

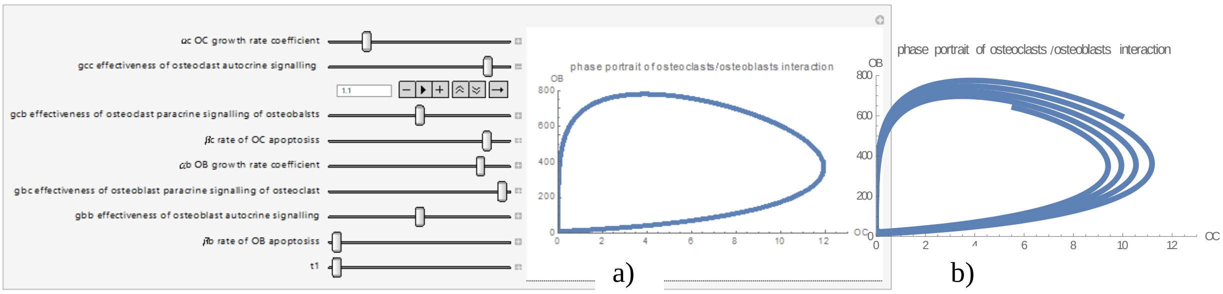

Figure 1: Phase portraits of OC-OB interaction dynamics for different γ_{11} parameter (effectiveness of osteoclast autocrine signalling) values: a) $\gamma_{11} = 1.1$ and b) $\gamma_{11} = 1.098$

Conclusions

Different types of external signals were observed in [3] and the nonlinear stability analysis [2] was used for obtaining parameter`s ranges for steady state solutions, the authors have proved that the modified model yields a positive non-oscillatory solution. This behavior of the solution is consistent with the bone remodeling cycle [1] returning to a quiescent state after three or five months. Additional quantitative and qualitative analysis of model sensibility to parameter`s changes have been presented with this paper results. Based on a simultaneous multi-parametric analysis it is possible to provide a parametric range where model exhibits periodic solutions and to analyze their effects on model dynamics. The usage of Mathematica program provides different visualization and animation technique of bone cell population model dynamics. As being nonlinear with power law terms γ_{ij} representing autocrine and paracrine signaling pathways in bone cell communication process system of ODEs (1) is highly sensitive on small changes of parameters (e.g. changes in system dynamics for only one parameter shifting is presented on Fig.1). The models explored in numerous numerical (in-silico) experiments also provide the more realistic approaches to understanding the development of interventions for patients with bone trauma and diseases, but also for those who want to prioritize the healthy and strong skeleton by applying suggested regular daily activities.

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