Simulation and analysis of bistability in osteochondrogenesis

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Introduction: During the endochondral ossification process, chondrocytes go through different states which can be roughly divided in two categories: the proliferative state (characterised by Sox9 expression) and the hypertrophic state (characterised by Runx2 expression). Understanding the transition between these main states is crucial to understand the bone formation process. However, the dynamic details are not yet fully elucidated.
In the proposed model, we focus on the dynamic interaction between the BMP and Wnt pathways [Eyckmans, 2009] and the way they determine the switch in osteogenic precursor cells between the Sox9 (proliferation) and Runx2 (hypertrophy) program via β-catenin [Zou, 2006].
Materials and Methods: Figure 1 shows a schematic representation of the proposed model which consists of two main parts. The first submodel is based on a previously developed model of the crosstalk between BMP and Wnt which will regulate the amount of β-catenin in the nucleus [Geris, 2010]. The second submodel focusses on the switch between the Runx2 and the Sox9. The bistable behaviour of this submodel has been studied thanks to a complete mathematical analysis, including an extensive screening [Yao, 2011] of the parameter space as well as phase plan and vector field analysis. Both submodels are systems of ordinary differential equations, based on the law of mass action and rate kinetics, and have been implemented in Matlab.
Results and discussion: Figure 2 shows the influence of BMP and Wnt on the transition from the proliferative program (Sox9 positive) to the hypertrophy program (Runx2 positive). Upon activation of the Wnt pathway, β catenin is upregulated and as a result the switch towards hypertrophy will take place, in agreement with experimental results available in the literature [Lui, 2010]. Further activation of BMP will inhibit the transition of β-catenin to the nucleus (only mutual inhibition between Wnt and BMP was incorporated in submodel 1) but the switch is irreversible. Additional simulations are being carried out and experimental work is underway to corroborate these preliminary results and to further investigate the model's parameter space.
References: Eyckmans et all, 2009, Journal of Cellular and Molecular Medecine, 14:1845-1856; Geris et al, 2010, Termis-EU Galway; Yao et al, 2011, Molecular Systems Biology, 7:485 ; Zou et al, 2006, Adv Exp Med Biol. 585:431-41 ; Lui,Andrade et al, 2010,Bone, 46(5)1380:1390

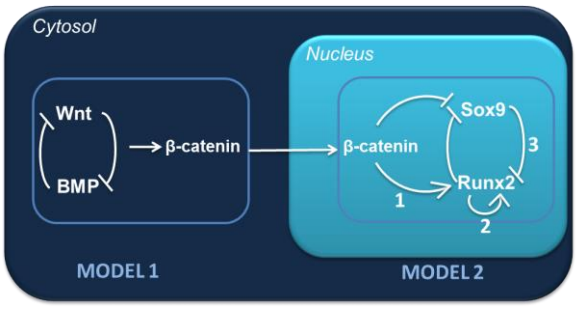

Figure 1: Schematic representation of the coupled model.

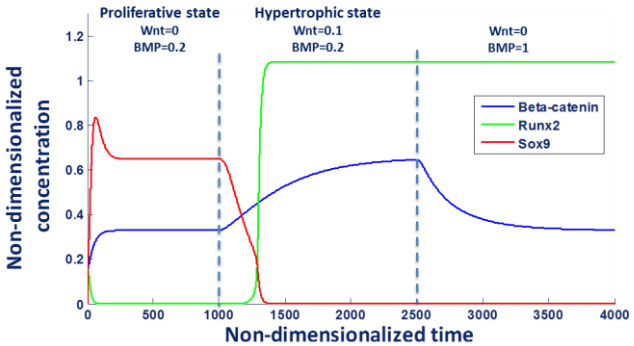

Figure 2: Evolution of relative quantities of Runx2, Sox9 and β-catenin for different values of BMP and Wnt.