

MATHEMATICAL MODELING OF ENDOCHONDRAL OSSIFICATION THROUGH MUTUAL INHIBITION AND BISTABILITY

Morgan Germain^{1,2}, Johan Kerkhofs^{1,2,3}, Liesbet Geris^{1,2}

¹Biomechanics Research Unit, Université de Liège, Chemin des Chevreuils 1, 4000 Liège, Belgium
²Prometheus, Division of Skeletal Tissue Engineering, K.U. Leuven, Herestraat 49, 3000 Leuven, Belgium
³Biomechanics section (BMe), KU Leuven, Celestijnenlaan 300C, 3001 Heverlee, Belgium

Introduction

Endochondral ossification is a complex process involving a myriad of influencing factors. Signalling pathways precisely navigate mesenchymal stem cells through the correct cascades. A detailed understanding of these cascades will enable us to develop efficient and robust tissue engineering products. A mathematical model is an interesting tool to study the different pathways involved in endochondral ossification as well as their interactions. In this model we focus on the influence of the BMP and Wnt pathways and the way they determine the switch between the Sox9 (proliferation) and Runx2 (hypertrophy) program via β -catenin [Zou, 2006].

Methods

Figure 1 shows a schematic representation of the proposed model, clearly showing the role of β -catenin as switch between the Runx2 and Sox9 program. The model 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 [Vandeput, 2010]. The second submodel focusses on the switch between the Runx2 and the Sox9 and has been mathematically designed to demonstrate bistable behaviour for specific parameter sets [Yao, 2011].

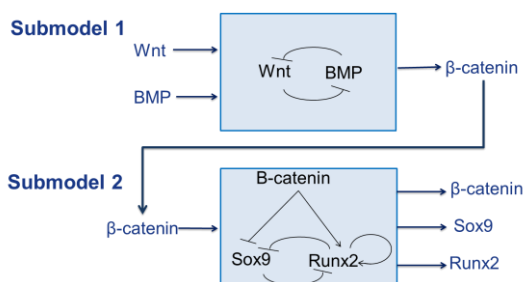


Figure 1: Schematic representation of the coupled model.

The model is a system of ordinary differential equations, based on mass action law and rate kinetics and has been implemented in Matlab. An extensive screening [Yao, 2011] of the parameter space has been carried out to define those

parameters sets for which submodel 2 exhibits bistable behaviour.

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. 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.

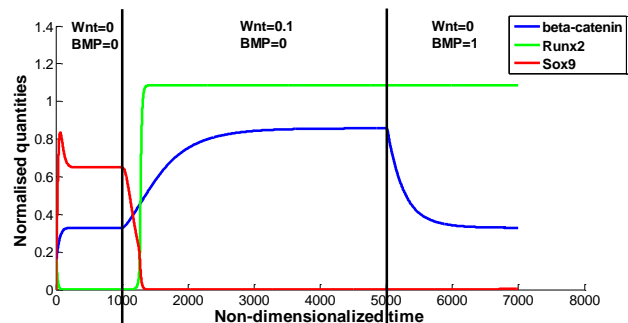


Figure 2: Evolution of relative quantities of Runx2, Sox9 and β -catenin for different values of BMP and Wnt.

Acknowledgements

This study was supported by the Belgian National Fund for Scientific Research (FNRS) and the European Research Council. This work is part of Prometheus, the Leuven R&D Division of Skeletal Tissue Engineering of the KU Leuven: <http://www.kuleuven.be/prometheus>.

References

- Vandeput 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.