Modeling the effect of the interaction between BMP and Wnt in osteochondroprogenitor cells

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INTRODUCTION

Background

- BMP and Wnt crucial for bone formation [1]
- Endochondral ossification : chondrocytes pass through a succession of states (proliferative and hypertrophic state)

Sox9-Runx2 switch and bistability

- Sox9 program is characteristic of the **proliferative state** and Runx2 program of the **hypertrophic sate**
- Runx2 and Sox9 inhibit each other
- β-catenin , downstream of Wnt and BMP, is a key factor in this mechanism

Aim of this study

- model the switch between Sox9 (proliferative) program and Runx2 (hypertrophic) program
- experimental validation

MATERIALS & METHODS

MODEL 1

- a **literature-based mathematical model** descibing BMP and Wnt pathways and various cross-talks [2]
- **mutual inhibition** between BMP and Wnt
- regulation of the amount of β-catenin in the nucleus
- **parameter values** derived from previous models [2] and experiments reported in literature [4]
- 19 variables, 49 parameters

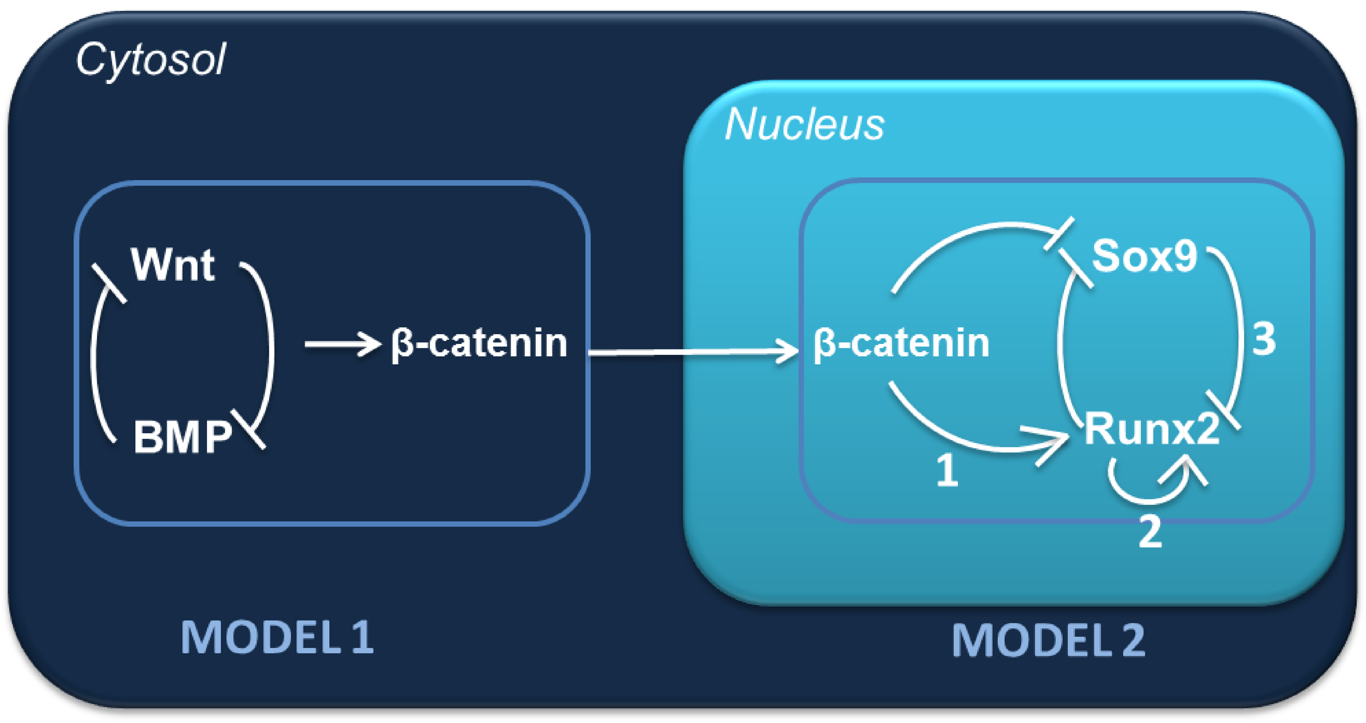

Figure 1 : Schematic representation of chondrocyte with indication of both models

MODEL 2

- a **literature-based mathematical model** describing the switch between Sox9 and Runx2
- **mutual inhibition** between Sox9 and Runx2
- **auto-activation** of Runx2
- **parameter values** by screening of parameter space to find parameter sets generating **bistable behavior** [3]
- 3 variables, 16 parameters

Ordinary Differential Equations (ODEs) describe the temporal evolution of the various model constituents (numbers refer to interactions in Figure 1)

$$\frac{d[Runx2]}{dt}=\left(\underbrace{\frac{[\beta_{cat}]^{n1}}{K_1^{n1}+[\beta_{cat}]^{n1}}}_{1}+\underbrace{\alpha_{Runx2}\frac{[Runx2]^{n2}}{K_2^{n2}+[Runx2]^{n2}}}_{2}\right)\underbrace{\frac{K_3^{n3}}{K_3^{n3}+[Sox9]^{n3}}}_{3}-\underbrace{[Runx2]}_{degradation}$$

RESULTS

- the model predicts that :
  - ✓ activation of Wnt upregulates β-catenin and provokes the switch between the Sox9 state and the Runx2 state
  - ✓ activation of BMP inhibits the transition of β-catenin to the nucleus but cannot provoke a switch from the Runx2 state towards the Sox9 state
  - ✓ two stable states (bistability) are obtained for appropriate parameter sets

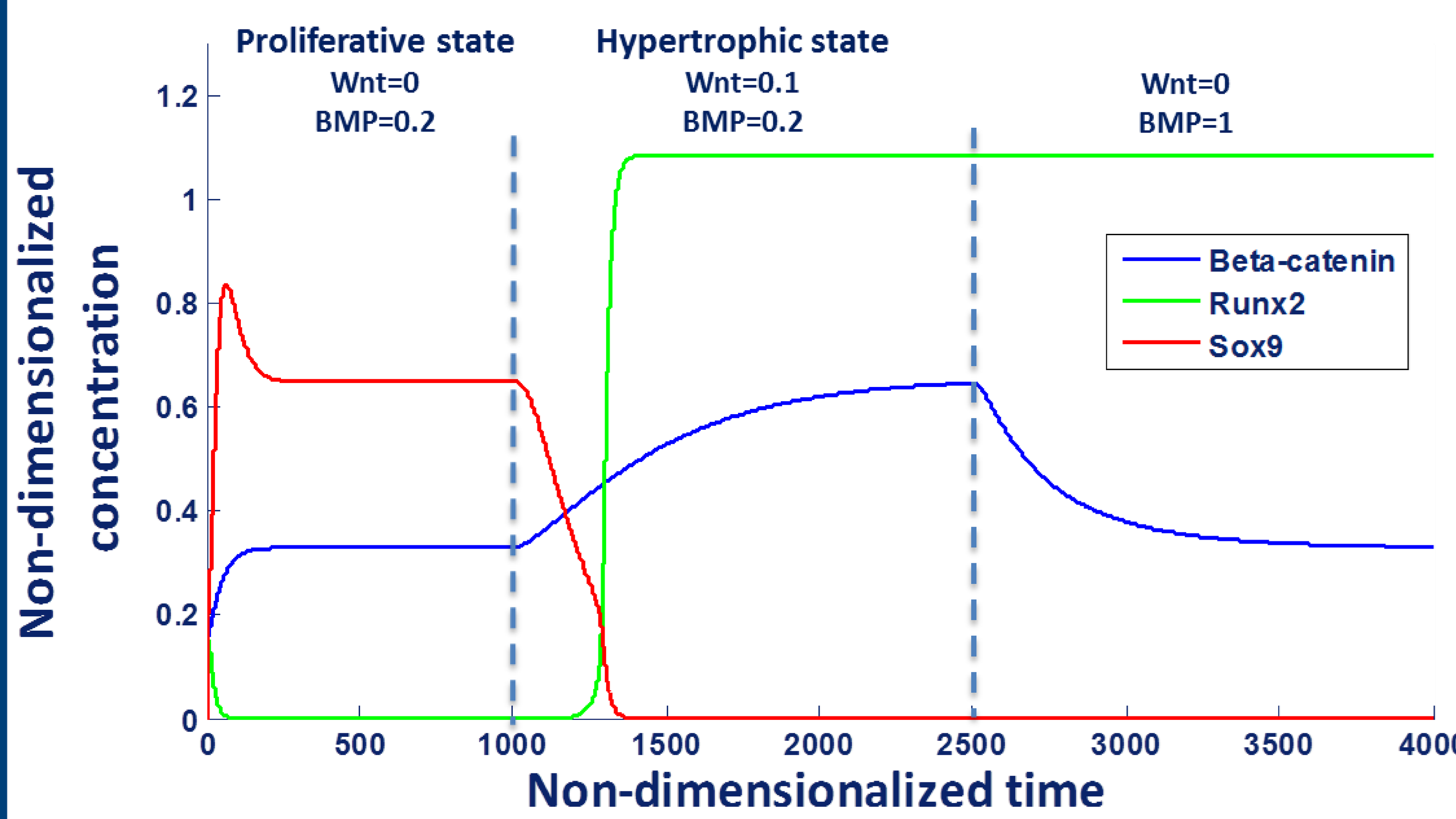

Figure 2 : Influence of Wnt and BMP on β-catenin, Sox9 and Runx2

DISCUSSION

- in absence of quantitative parameter information, the ODE model presented here provides qualitative predictions on changes in the concentrations of all modelled components
- the model is able to reproduce the switch between the Sox9 program and the Runx2 program for specific parameter sets
- the model behavior is in concordance with experimental results present in the literature [5]
- mathematical models can be used to enhance our understanding of signaling cascades and their interactions

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This work is part of Prometheus, the R&D Division of Skeletal Tissue Engineering of the KU Leuven: http://www.kuleuven.be/prometheus.
We acknowledge the European Research Council under the European Union's Seventh Framework Program (FP7/2007-2013)/ERC grant agreement n°279100.