SIMULATION AND ANALYSIS OF RECEPTOR DYNAMICS IN A BMP REGULATORY NETWORK

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INTRODUCTION

BMPs

- *Bone Morphogenetic Proteins (*BMPs) are crucial for bone formation
- *BMPs* signal through two transmembrane receptors: type 1 (R1) and type 2 (R2) receptor
- Two pathways : Canonical (C) and Non-canonical (NC)
- The final complex ligand-receptors (LR1R2) can be formed in two different ways
- Way of recruiting the receptors determines the activated pathway [1,2]

FOP

- *Fibrodysplasia Ossificans Progressiva (FOP)* is a disease that causes heterotopic ossification of soft tissues [3,4]
- FOP is linked to a constitutive activation of Alk2 (type 2 BMP receptor)
- The effect is coupled
  - ✓ Non-enzymatic cooperation with R2 receptors
  - ✓ Disruption of the non-canonical pathway

Aim of this study

- Simulation and analysis of a complete BMP model :
  - ✓ receptor traffic
  - ✓ both signaling pathways (C and NC)
- Simulation of FOP conditions to identify the key factors in this disease

MATERIALS & METHODS

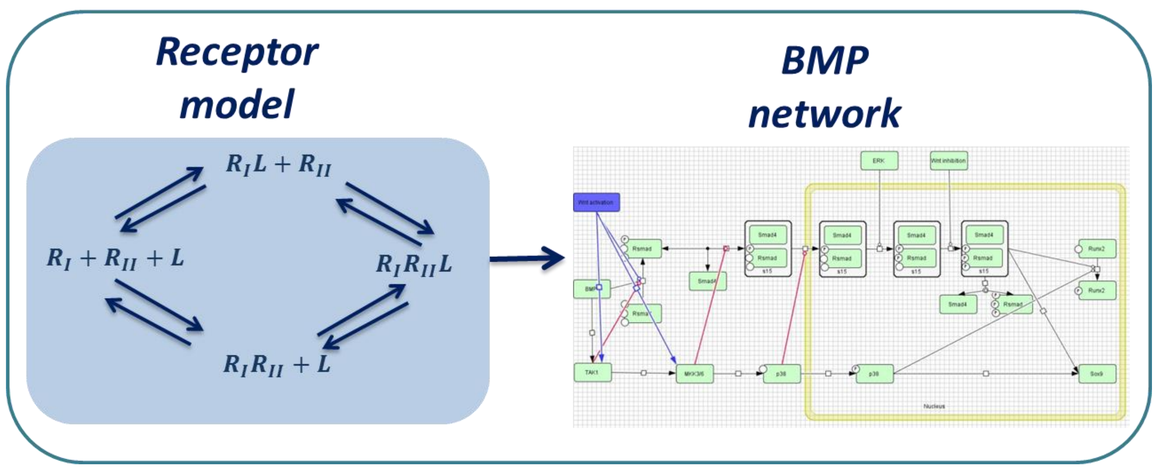

Figure 1 : Schematic representation of the model

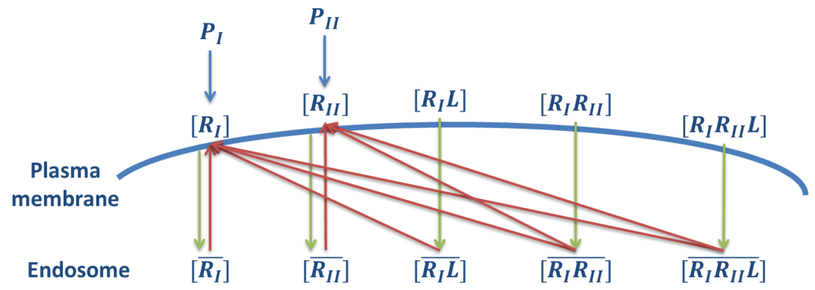

Figure 2 : Schematic representation of the traffic between plasma membrane and endosomes

- **Two literature-based mathematical models :**
  - ✓ **Receptors model :** How receptors binds to BMP and amongst themselves [2]
    - ❑ **Two ways** of binding modeled
    - ❑ 10 variables, 17 parameters
    - ❑ **Traffic** between plasma membrane and the endosomes also investigated (Figure 2) [5]
  - ✓ **BMP network :** The non-canonical and the canonical pathways [6,7]
    - ❑ Various **crosstalks** between both pathways modeled
    - ❑ 12 variables, 23 parameters
- **Parameter values** derived from previous models [2], based on experiments
- **Ordinary Differential Equations (ODEs)** describe the temporal evolution of the various model constituents, e.g.:

$$\frac{d[LR1R2]}{dt} = k_1[LR1][R2] + k_2L[R1R2] - k_3[LR1R2]$$

where k_3 regroups different terms (degradation, internalization, recycling,…).

- Model implemented and simulated in **Matlab**

RESULTS

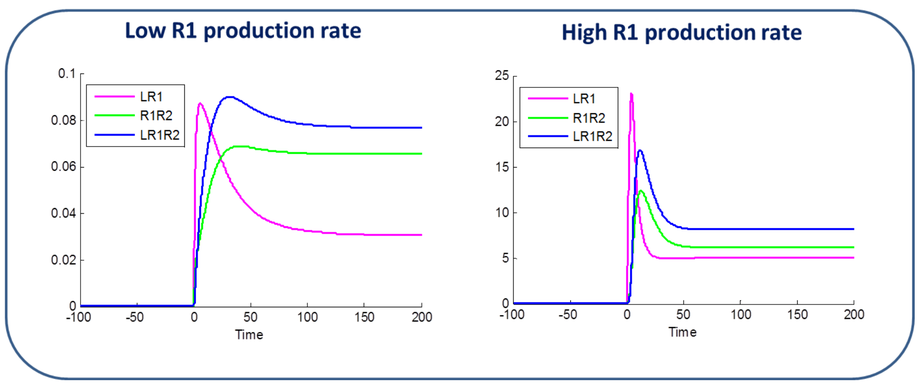

Figure 3 : Evolution over time of relative quantities of three key factors of the receptor dynamics model : **LR1** (the NC pathway indicator), **R1R2** (the C pathway indicator)and **LR1R2 (**the final receptor-ligand complex) for low (left) and high (right) R1 production rates (PR1)

- **Dynamics simulation** by adding ligand (BMP) at t=0
- **FOP** *:*
  - ✓ simulated by the over-expression or higher activation of the receptor R1
  - ✓ disruption of the NC pathway experimentally observed
- **The model predicts** that
  - ✓ the rate of R1 production determines the preference for either the canonical or the non-canonical pathway
  - ✓ the ratio of the peak of the NC pathway to the peak of the C pathway is inversely related to the PR1
  - ✓ the ratio of their steady-states is bigger when PR1 is higher

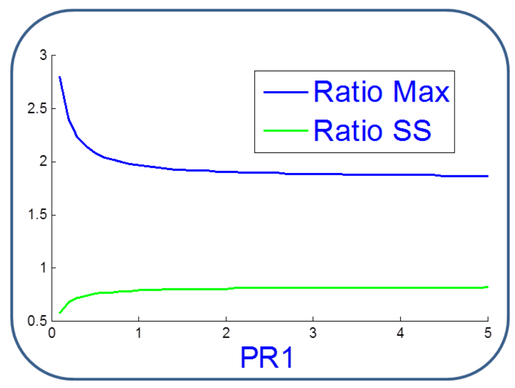

Figure 4 : Evolution of the ratio LR1/R1R2 (indicative for the ratio NC/C) for different values of R1 production rates. Ratios are shown for both peak values and steady-state values

DISCUSSION

- In absence of quantitative parameter information, the presented ODE model provides qualitative predictions on changes in the concentrations of all modelled components
- The model is able to capture experimental observations such as the choice of different BMP pathways BUT is not able to correctly reproduce the disruption of the non-canonical pathway in FOP cells suggesting that back-up pathways are activated (hypothesized in the field)
- Experimental work is underway to guide further model development

REFERENCES

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