

Simulation and Analysis of Bistability in Osteochondroprogenitor Cells

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

¹Prometheus, Division of Skeletal Tissue Engineering, KU Leuven, Belgium ; ² Biomechanics Research Unit, Université de Liège, Belgium ; ³ Biomechanics section (BMe), KU Leuven, Belgium



KU LEUVEN

Université de Liège 

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 state**
- 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 describing 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

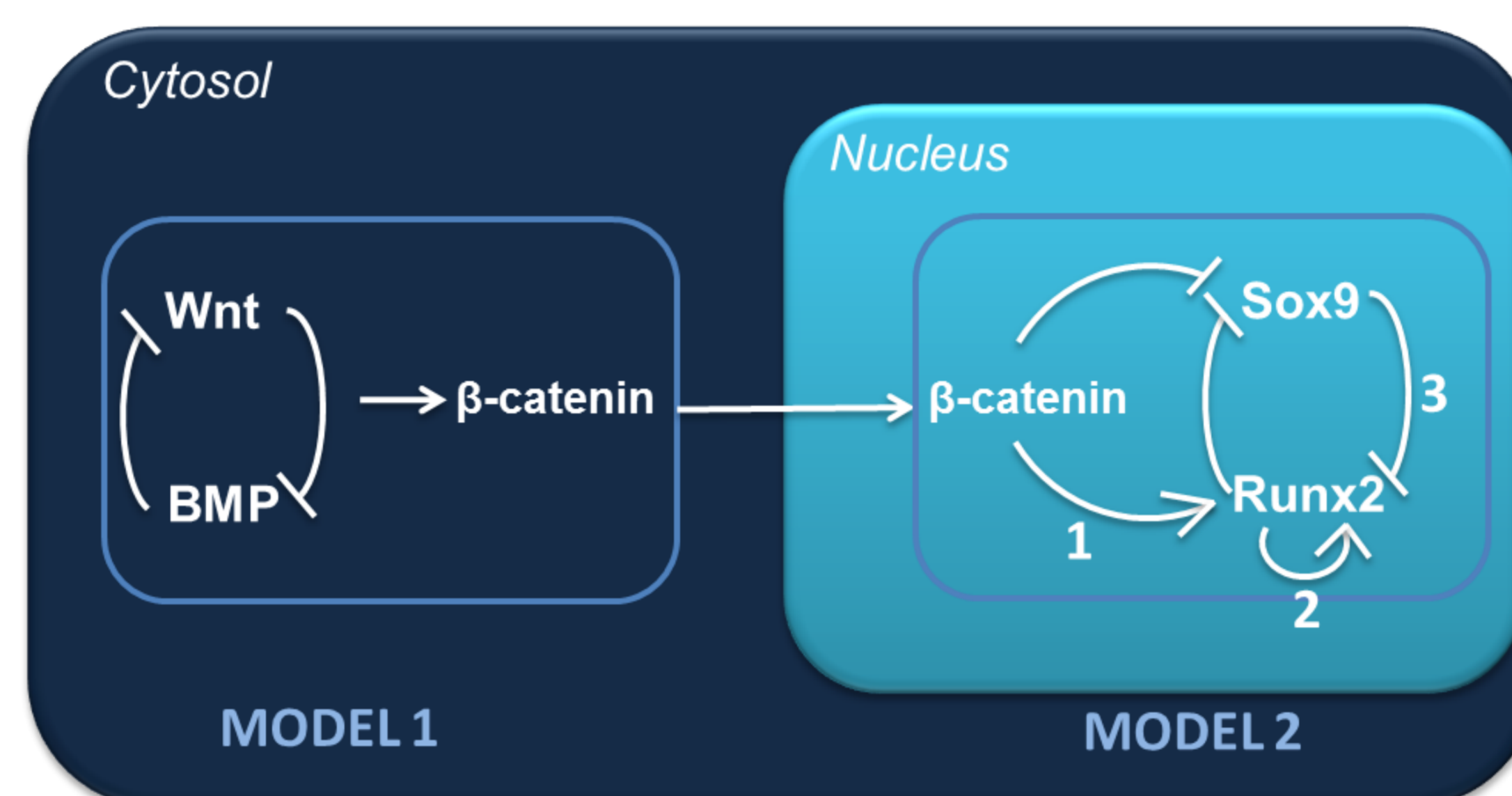


Figure 1 : Schematic representation of chondrocyte with indication of both models

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)

$$\frac{d[Runx2]}{dt} = \underbrace{\left(\frac{[\beta_{cat}]^{n1}}{K_1^{n1} + [\beta_{cat}]^{n1}} \right)}_1 + \underbrace{\alpha_{Runx2} \frac{[Runx2]^{n2}}{K_2^{n2} + [Runx2]^{n2}}}_{2} \underbrace{\frac{K_3^{n3}}{K_3^{n3} + [Sox9]^{n3}}}_{3} - \underbrace{[Runx2]}_{\text{degradation}}$$

RESULTS

The model predicts that :

- ✓ activation of Wnt upregulates β -catenin and provokes switch between Sox9 and Runx2 state
- ✓ activation of BMP inhibits 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

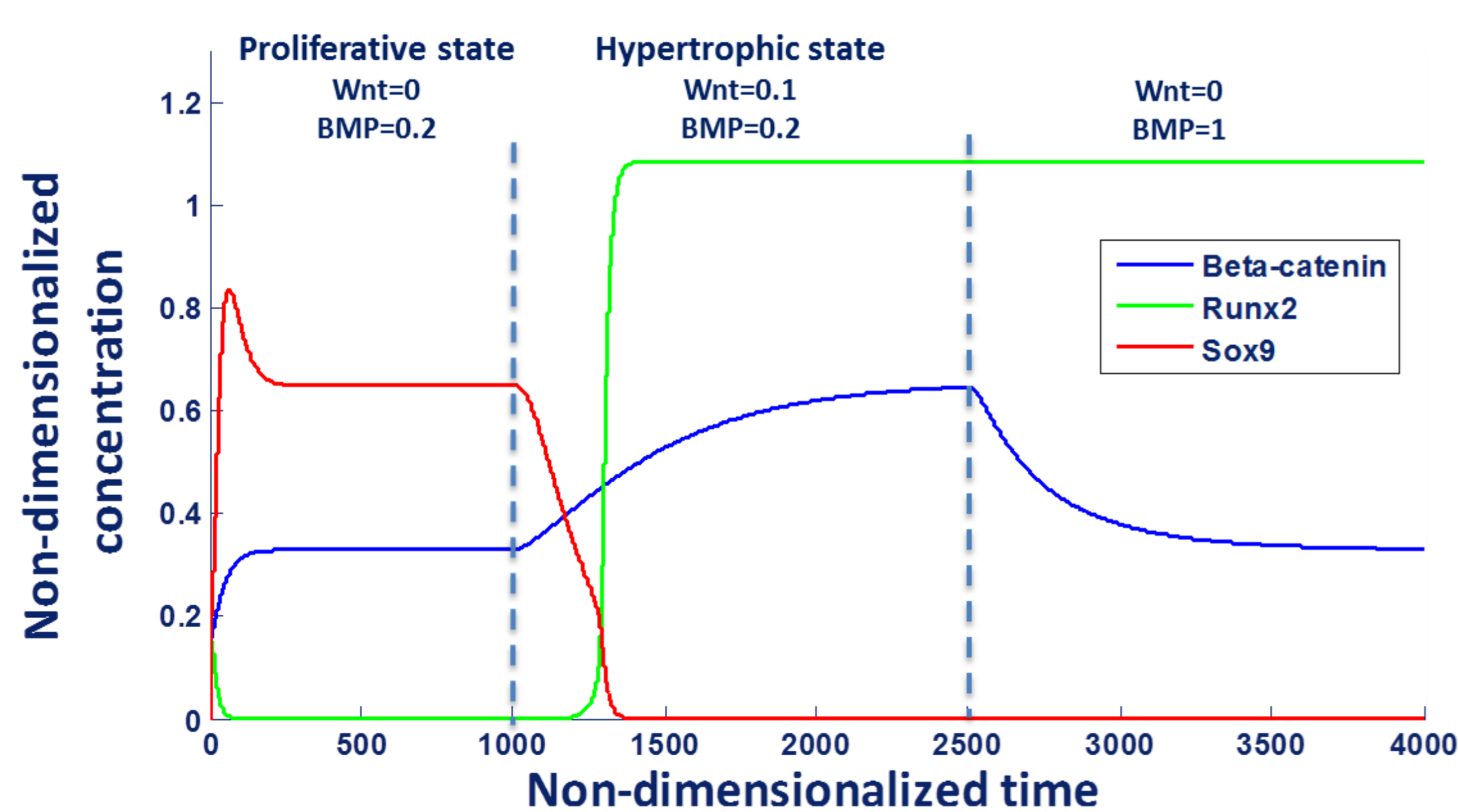


Figure 2 : Influence of Wnt and BMP on β -catenin, Sox9 and Runx2

MATHEMATICAL ANALYSIS

Bistability can be checked through a mathematical analysis :

- ✓ Isoclines and vector field
- ✓ 3 steady states for a low value of β -catenin : 2 stable and 1 unstable \rightarrow bistability
- ✓ 1 stable steady state for a high value of β -catenin : Runx2 state

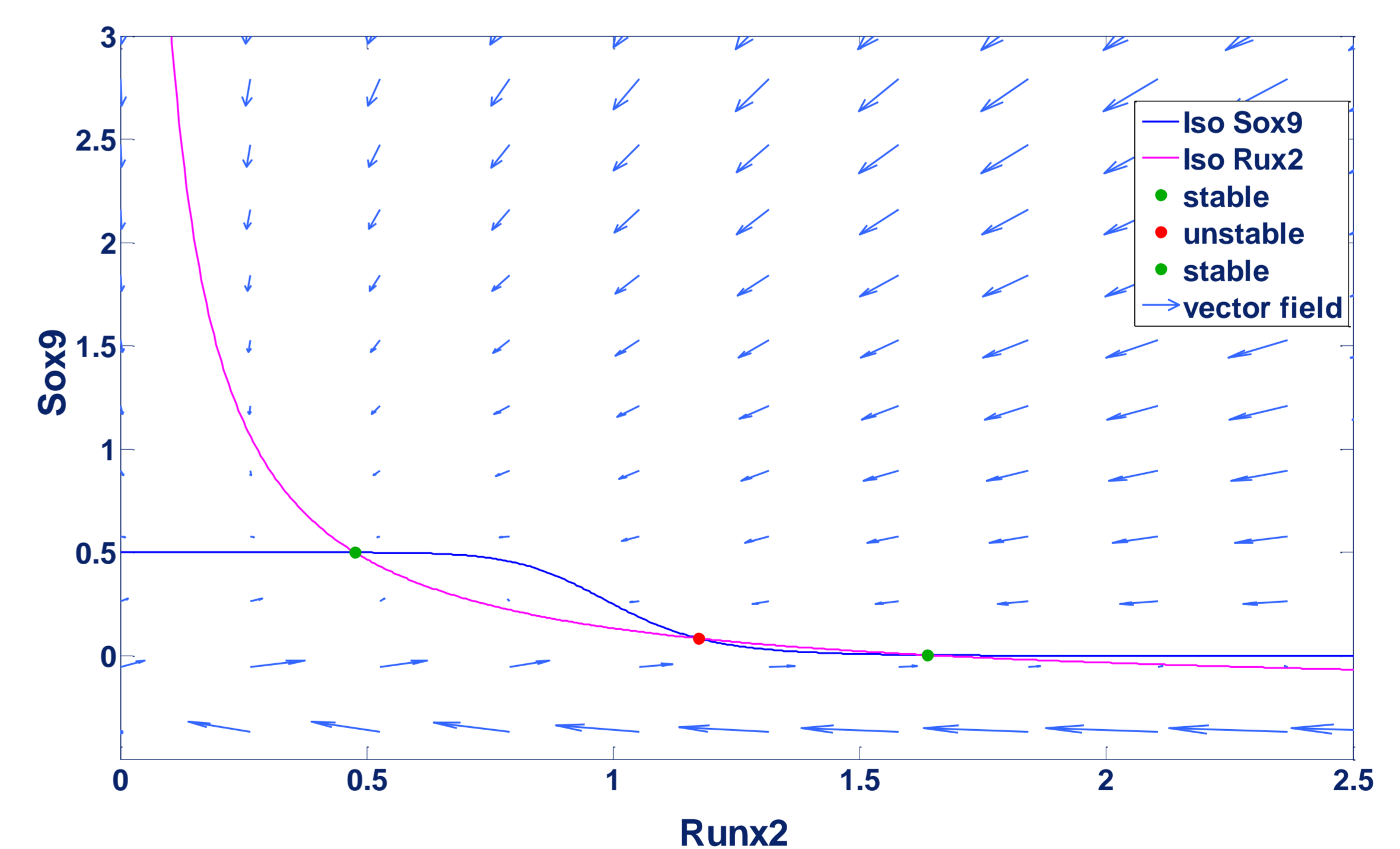


Figure 3 : Phase plane for the bistable case

DISCUSSION

- in absence of quantitative parameter information, the ODE model provides qualitative predictions on changes in the concentrations of all modelled components
- reproduction of switch between Sox9 and Runx2 program for specific parameter sets
- model behavior is in concordance with experimental results [5]

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CONTACT

Université de Liège, Belgium,

morgan.germain@ulg.ac.be
liesbet.geris@ulg.ac.be