# Mathematical modelling of bone formation based on local $Ca^{2+}$ concentrations in calcium phosphate scaffolds

V. Manhas[1,3,5], Y. Guyot[1,5], Y.C. Chai[2,5], G. Kerckhofs[1,4,5], A. Carlier[1,3,5], J. Schrooten[4,5] and L. Geris[1,3,5]

[1]Biomechanics Research Unit, University of Liège, Liège, Belgium; [2]Tissue Engineering Laboratory, Skeletal Biology and Engineering Research Center, KU Leuven, Belgium; [3]Department of Mechanical Engineering, Division of Biomechanics Section, KU Leuven, Belgium; [4]Department of Metallurgy and Materials Engineering, KU Leuven, Belgium; [5]Prometheus, Division of Skeletal Tissue Engineering, KU Leuven, Belgium

## INTRODUCTION

- In tissue engineering (TE) applications, scaffolds act as carriers for cells and growth factors that restore functionality of an organ.
- Since the 1960s, calcium phosphate (CaP) has proven to be an excellent bone substitute material [1].
- However, complexity of the *in vitro* and *in vivo* behavior of these scaffolds has not been elucidated completely.
- Computational models can help us to understand this complexity, allowing improvement in scaffold design.

**The aim of this study is to computationally determine the local $Ca^{2+}$ concentrations of different clinical grade CaP scaffold types and subsequently represent its effect on *in vivo* bone regeneration.**

## MATERIALS & METHODS

- The nanofocus X-ray computed tomography (nanoCT) images are obtained to extract the scaffold geometries (fig.1A).
- The scaffold morphology is then defined in the finite element (FE) domain (fig.1B).
- The level-set method (LSM), a numerical technique is used to track scaffold shape during the bone formation process (fig. 3).

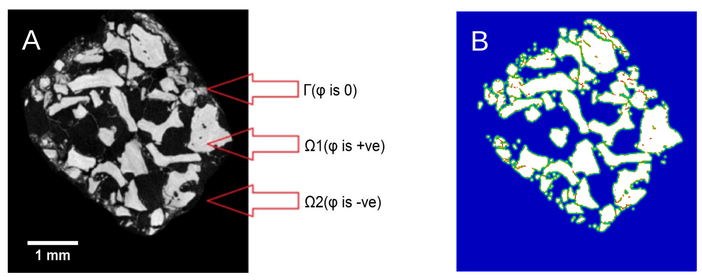


Figure 1: A. NanoCT image of CaP granules in the scaffold and B. Scaffold morphology defined in FE domain (right)

- The model is developed as part of design and manufacturing strategy to investigate the cell-carrier combinations for optimum bone formation.
- Both, the level-set equation and the linear and non-linear PDEs are implemented in FreeFEM++, a free C++ based finite element solver.

## MODEL SETUP

A previously developed model of calcium driven bone regeneration (Carlier et al 2011) has been altered to account for novel insights. The equations describe densities of cells (mesenchymal stem cells (MSCs) and osteoblasts), osteogenic growth factors, collagen matrix, mineralization and calcium concentration.

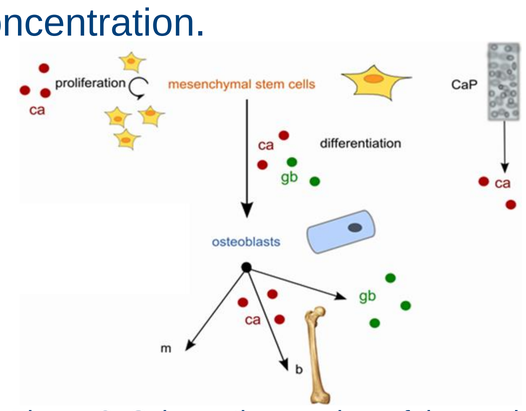


Figure 2: Schematic overview of the model

The local growth factor density and $Ca^{2+}$ concentration in the system influence the behaviour of cells (proliferation, differentiation, diffusion and apoptosis). The growth factors are produced by both MSCs and osteoblasts whereas production of collagen matrix is dependent only on osteoblasts. The bone formation is dependent on osteoblasts & local calcium concentration (see figure 2). At the start of the simulation, there are MSCs ($c_{m,\,ini} = 10^6 cells/ml$), growth factors ($g_{b,\,ini} = 1.5\ \mu g/ml$) and collagen matrix ($m_{ini} = 0.001\ g/ml$). For $Ca^{2+}$, various physiological values ranging from low to high are used.

## RESULTS

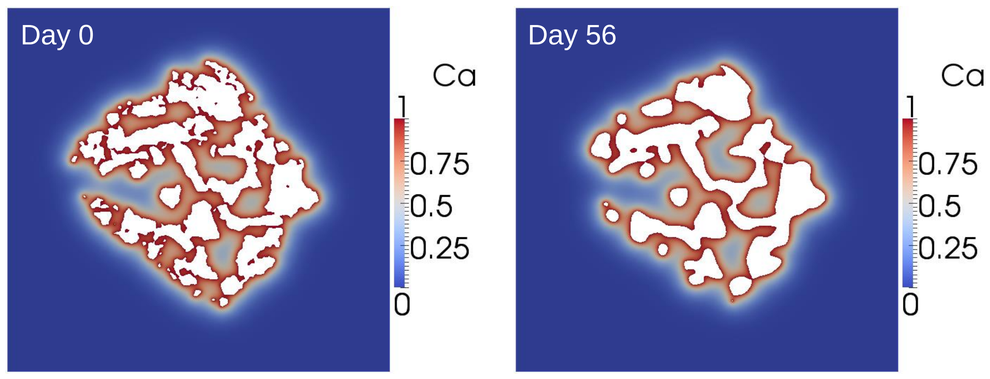


Figure 3: Shrinking of the scaffold during bone formation process

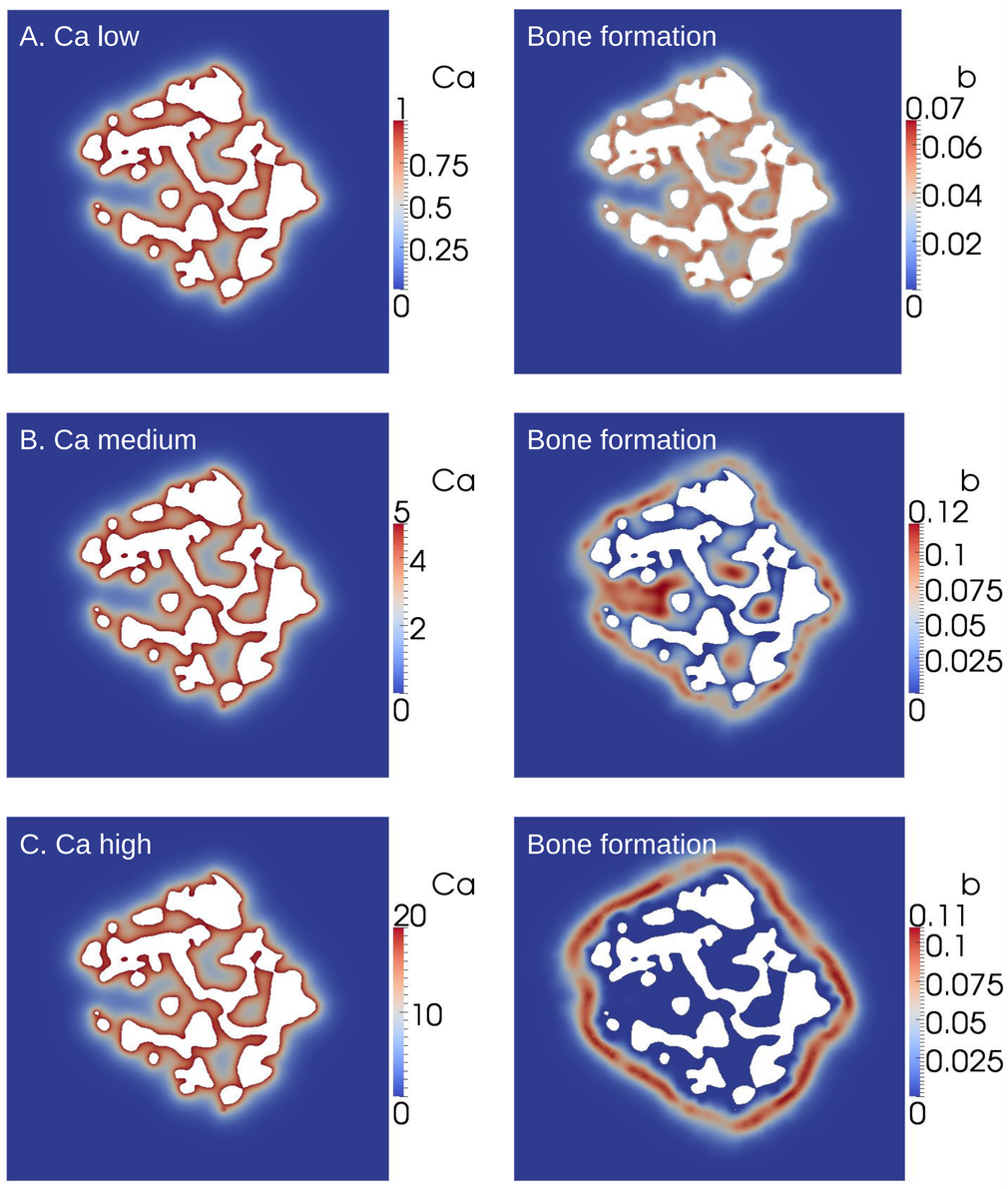


Figure 4: A. Bone formation when Ca is low, B. Bone formation when Ca is medium, C. Bone formation when Ca is high

## DISCUSSION

- The model is able to reproduce the sequential events observed experimentally (not shown here) during bone regeneration: (a) proliferation, (b) differentiation, (c) collagen production & (d) mineralization.
- The model is also able to simulate the influence of local $Ca^{2+}$ on bone regeneration (fig. 4 A,B,C).

## CONCLUSION

- The proposed model is an interesting computational tool to investigate the interactions between CaP based biomaterials and osteogenic cells.
- However, dedicated in vivo and in vitro experiments are ongoing in our lab to validate the in silico results.

## REFERENCES

[1] Carlier et al, Acta Biomaterialia, 7:3573-3585, 2011.

## CONTACT DETAILS

Varun Manhas / Liesbet Geris
Biomechanics Research Unit, University of Liege
liesbet.geris@ulg.ac.be

This work is part of Prometheus, the KU Leuven R&D Division of Skeletal Tissue Engineering (http://www.kuleuven.be/prometheus).
The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreements n. 279100; from the Belgian National Fund for Scientific Research (FNRS) Grant FRFC 2.4564.12 and from the special research fund of the KU Leuven (GOA/13/016).