THE ROLE OF ANATOMICAL LOCATION IN SCAFFOLD-INDUCED HEALING OF CRANIOFACIAL BONE DEFECTS

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Introduction

When a bone fractures, successful healing is usually achieved within weeks. However, fracture severity and anatomical location can lead to delayed- or non-healing. We developed a 3D *in silico* model of bone regeneration and used it to investigate the influence of a scaffold produced using melt electrowriting (MEW) and coated (or not) with cells or growth factors (GF) as treatment strategy in craniofacial bone defects, and to explore the role of the defect anatomical location (mandibular versus calvarial).

Methods

***In silico* model.** We developed a 3D *in silico* model in FreeFEM [1], following an existing multiscale bioregulatory 2D model of bone fracture healing [2]. Our model captures biological processes across time and space scales, simulating osteogenesis and sprouting angiogenesis. At the tissue/cellular level, the spatiotemporal evolution of biochemical factors, cells and matrices is described using a non-linear system of taxis-diffusion-reaction partial differential equations. At the (intra)cellular level, the developing vasculature is simulated with discrete endothelial cells, regulated individually by one ordinary differential equation representing its intracellular module. Suitable initial and boundary conditions ensure the existence, uniqueness and non-negativity of the solution.

Domain. We investigated two types of craniofacial defects: calvarial and mandibular. The geometrical domains (Fig. 1) were deduced from critical-sized defects in rabbits and generated as finite element meshes. Due to symmetry, only one-fourth of each domain (blue region in Fig. 1) was simulated.

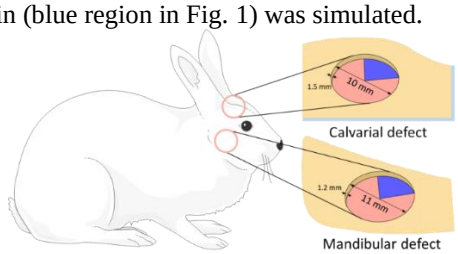

Figure 1: Schematic representation of the craniofacial bone defects: calvarial (top) and mandibular (bottom).

Implementation details. The healing progress of the two craniofacial defects was investigated with and without the application of the MEW scaffold. Migration of skeletal progenitor cells (SPCs) and vascular restoration were assumed from all domain surfaces (top, bottom and lateral) for the calvarial defect due to the presence of the periosteum and the dura mater. For the mandibular defect, SPCs migration was assumed only from the lateral surface. The MEW scaffold was simulated with initial and/or boundary conditions representing different burst-release profiles of cells and/or GF from the scaffold into the bone defect. We used Bayesian optimization to optimize the model parameters as pre-validation step.

Results

Our model adequately captured the biological processes of bone regeneration for the two types of craniofacial defects – in line with their developmental origin: intramembranous ossification for the calvarial defect due to a fast restoration of the vasculature, and intramembranous and endochondral ossification for the mandibular defect due to a more prolonged hypoxic injury site (results not shown). Our *in silico* predictions were compared with *in vivo* results [3] at 4 weeks post surgery to investigate the MEW scaffold as treatment. The *in vivo* mandibular defect showed no significant difference in bone volume (Fig. 2A), which led to non-healing. We used our model to explore adequate GF concentrations to load onto the MEW scaffold such that (delayed) healing was achieved (Fig. 2B).

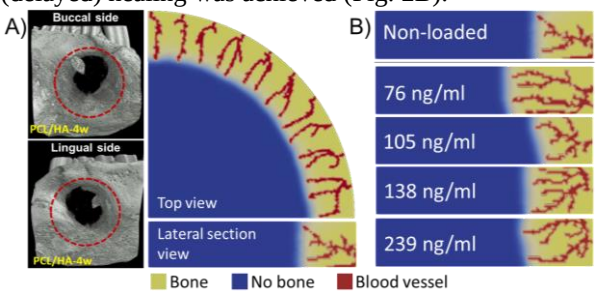

Figure 2: Mandibular defect at 4 weeks. (A) In vivo *(left) vs.* in silico *(right) results with non-loaded scaffold. (B)* In silico *results for several GF-loaded scaffolds, which predicted more favorable healing outcomes.*

Discussion

Our *in silico* model captured the biological reality of bone regeneration for different anatomical locations, allowing us to identify the most impactful conditions *in vivo* and to optimize tissue-engineered scaffolds.

References

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