

Understanding bone healing: combining *in silico* and *in vivo* approaches

K Ito¹

¹ [Department of Biomedical Engineering, Eindhoven University of Technology, The Netherlands](#)

INTRODUCTION: Most bone fractures today are well treated with current implants and heal uneventfully. However, complications do persist, e.g. 5-10% of all fractures in humans do not heal in a timely manner [1]. Furthermore, incidence of delayed unions may increase due to the aging population and diminished regenerative capacity of the elderly. Clinical factors such as general health, trauma severity, surgery, fixation and post-operative care all interact in determining the biological and biomechanical conditions of the healing fracture which in turn then determines if it will heal in a timely manner, if at all. Thus, in order to rationally develop treatment strategies to overcome delayed- or non-unions, we first need to understand this complex interaction involved in the healing process.

Secondary or indirect bone healing is a regenerative process involving both intramembranous and endochondral ossification. During ossification, progenitor cells become activated, proliferate, apoptose, migrate and differentiate into various cell phenotypes. Mature cells also react similarly as well as synthesize and remodel their tissue specific matrices. In all of these processes, the active component is the cell which is known to be sensitive to its physical environment.

A decade ago, Prendergast and Huiskes first proposed that mesenchymal progenitor cell differentiation can be mechano-regulated by the local combined magnitude of interstitial fluid flow velocity and tissue shear strain [2]. We hypothesize that this mechanoregulation principal is also applicable to fracture healing. Our approach to demonstrate this has been to develop a computational model, based on this principal and established cell based processes, capable of simulating the biological process of indirect fracture healing and determine if this model could also be corroborated again *in vivo* experiments of abnormal fracture or bone healing.

MODEL: First a 3D finite element model (FEM) of an idealized mid-diaphyseal fracture in an ovine tibia reduced with a small gap was developed. The marrow, cortical bone and an initial callus of granulation tissue was modelled with poroelastic elements and material properties from the literature. This FEM was then embedded in another

model where cellular processes were quantitatively described with partial differential equations, logical rules and parameter values derived from *in vitro* and *in vivo* experiments in the literature [3].

RESULTS: The model was able to correctly simulate the temporal and spatial distribution of tissues during normal fracture healing under axial loading. It was also able to simulate delayed and non-union formation with overloading as observed by Claes et al. [4] as well as other abnormal healing conditions such as delayed healing due to periosteal damage and genetic deficiencies in cartilage resorption [5-6].

To challenge the model it was also corroborated against *in vivo* experimental conditions of pure torsional interfragmentary motion. Similar to the *in vivo* results, the model simulated a unique spatial distribution of intercortical gap bone formation. Finally, the underlying model was adapted to simulate distraction osteogenesis and compared to an *in vivo* experiment in sheep [7]. The model was not only able to simulate the experimental results but also to correctly capture the affect of distraction rate and frequency on bone formation.

CONCLUSIONS: These comparisons of *in silico* and *in vivo* results support the validity of the mechanoregulation theory first proposed by Prendergast and Huiskes and suggest that *in silico* models of fracture healing may be ready to be used for implant design and in the clinics in the near future.

REFERENCES: ¹A. Praemer, et al (1992) AAOS. ²P. Prendergast et al (1997) *J Biomech.* ³H. Isaksson et al (2008) *J Theor Biol.* ⁴L. Claes et al (1997) *J Orthop Res.* ⁵C. Colnot et al (2003) *Develop.* ⁶N. Kosaki et al (2007) *Biochem Biophys Res Commun.* ⁷U.H. Brunner et al (1994) *Clin Orthop Rel Res.*

ACKNOWLEDGEMENTS: This abstract was based mostly on the work conducted during the PhD research of Dr. Hanna Isaksson.