

Multi-scale modelling of physiological processes in bone regeneration and tissue engineering

Mathematical models of physiological processes across the scales can be used as a research tool in Tissue Engineering (TE). Continuum and hybrid models at tissue/organ level have been developed to simulate normal and impaired fracture cases and to design potential treatment strategies for the latter in silico. Cell level (agent based) models that are currently under development allow for incorporation of a mechanistic description of cell cycle events, intercellular forces and intracellular signals. This modelling level is particularly suited to investigate the major constituents of cell aggregate behaviour. Finally, models at the gene/protein level provide an interesting tool to investigate properties of individual signalling cascades and cross talks between pathways. Different modelling types such as Ordinary Differential Equations and Boolean Network models are used depending on the biological question at hand.

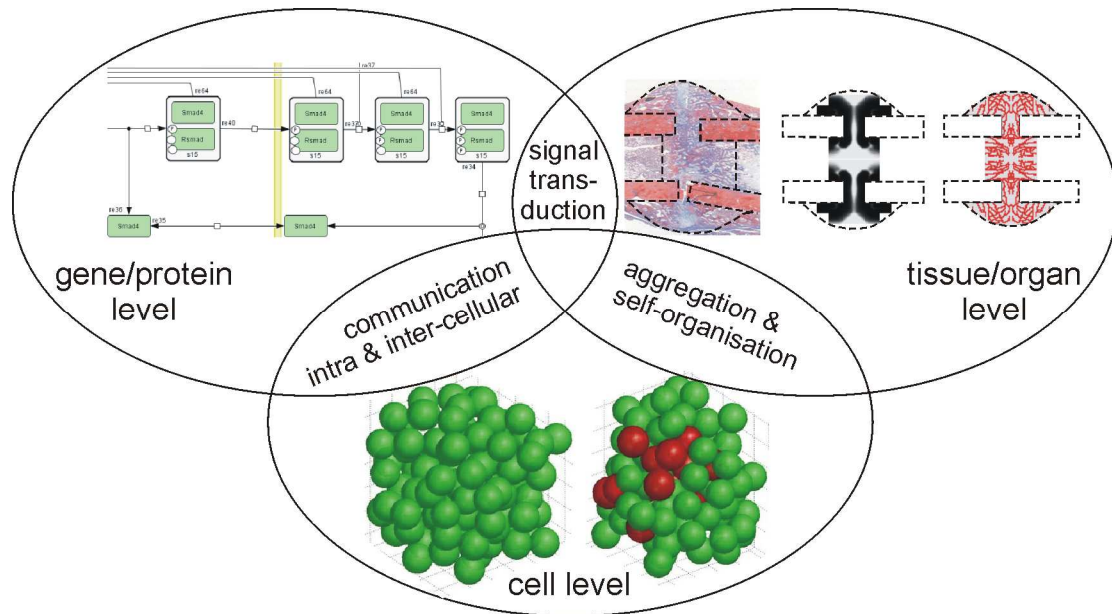


Figure 1: Overview of different modelling scales

Bone regeneration and tissue engineering are interdisciplinary research topics and involves many themes. At the department of Aerospace & Mechanical Engineering, specific attention is paid to the following themes:

- **Modelling of bone fracture healing**

Bone is a remarkable material as, under most circumstances, it is capable of truly regenerating itself, whereas soft tissue wound healing results in scar formation. However, despite bone’s natural healing capacity and the extensive amount of research that has been conducted in this area, 5–10 per cent of the fractures develop into delayed unions or even non-unions, costing society large amounts of money. This cost is sure to rise in the future, in light of the ageing population and the prediction that 40 per cent of all postmenopausal women will suffer one or more fractures in their remaining life time. Therefore, prevention and effective treatment are highly desirable. A mathematical model has been developed, describing certain key steps in the fracture healing process, such as intramembranous and endochondral ossification, the actions and interactions of growth factors and cells, the presence of vasculature and the influence of mechanical loading. This model can be used in silico test various hypothesis and mechanisms of failure and design treatment strategies. Ongoing model developments include the angiogenic and mechanical aspects of the model as well



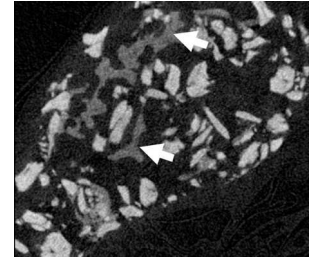
as an optimization of the model implementation software.

BRU (biomechanics research unit)

External partner: Technische Universität Darmstadt (<http://www3.mathematik.tu-darmstadt.de/ags/numerik-und-wissenschaftliches-rechnen/home.html>)

- **Multi-scale modelling in bone tissue engineering: from biomaterials to intracellular signalling cascades via the cell.**

Bone tissue engineering (TE) is a promising alternative for the treatment of large bone defects. In the current state of the art scaffolds are seeded with cells and subsequently implanted. Despite some successful studies, bone TE to date still suffers from unpredictable and qualitatively inferior results. To increase both quality and reproducibility, we have to better understand the mechanisms by which bone can be regenerated. Given the increasing evidence that embryonic signalling pathways are recapitulated during tissue regeneration, TE strategies should aim to stimulate those embryonic signalling cascades when developing a tissue construct. As these intracellular signalling networks are complex due to the massive amount of influencing factors (not only other intracellular signals but also e.g. extracellular metabolic signals), mathematical modelling can provide a tool to qualitatively and quantitatively investigate these biological phenomena and design the experimental conditions to optimize both quality and robustness of the tissue construct's production process. This project aims to develop such a multi-scale mathematical model for the study of cell-scaffold interactions by combining a tissue level model that describes the spatio-temporal evolution of the biomaterial, extracellular matrix, blood vessels, cells and growth factors with an intracellular model that describes the activation of relevant signalling cascades.

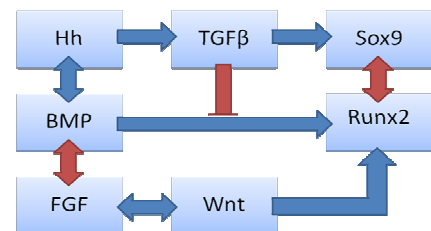


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- **Modelling of Gene Networks for Steering of Biomimetic Production Processes in Tissue Engineering**

This project aims to increase the predictability and the consistency of the behaviour of TE products by means of the development and application of Boolean gene network models. Such models can assist in establishing, optimising and steering biomimetic TE production processes. A Boolean model is developed to identify and elucidate vital developmental signalling pathways and their interactions in the developmental process of endochondral ossification. Once the key players as well as genes that can influence them are highlighted (in vivo), their expression will be investigated by in vitro cultures of several cell types. The in vitro process will be assessed on whether, and to what extent, the desired developmental pathways (i.e. endochondral ossification as described by the in vivo Boolean model) are being followed. The characterisation of the cell population, using the Boolean model, would give an indication of the cell state and their ability to induce ossification in vivo, and in this regard the parameters are useful to control and observe the in vitro process. The Boolean model can hence determine whether the cell population is evolving in the desired direction and as such provides valuable feedback for achieving an improved product consistency.



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