MINISYMPOSIUM

EXPLORING THE TISSUE REGENERATION PROCESSES THROUGH MATHEMATICAL MODELLING

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In mammals, tissue's natural response to injury or disease is associated with a wound healing process leading to scar formation. Scar tissue is often formed at the expense of normal tissue regeneration, which corresponds to the complete recovery of the system properties and functionalities after injury. However, some organisms are able to regenerate after injury, and the ability to heal is developed differently throughout diverse species: from simple tissue repair to the regeneration of complete organs (as shown in axolotls for instance). One of the major challenges in regenerative medicine is to trigger tissue regeneration by therapeutically manipulating its natural ability to form a scar at the time of injury or disease. Understanding the mechanisms at play in both scar formation and regeneration is therefore of major importance in tissue engineering, regenerative medicine and various diseases.

If nowadays, research highlights a deeper understanding of the molecular biology of wound healing, of the complex interplay of cells and the distinct influence of the different cytokines and growth factors, the mechanisms underlying tissue repair and its failure to heal are still poorly understood, and current therapies are limited.

The goal of this mini-symposium is to bring together speakers from different backgrounds to offer a state of the art view on regeneration and scar formation studies through mathematical modelling including lab experiments, data driven modelling, imaging softwares and theoretical and numerical analysis. The regeneration/scar formation mechanisms will be explored at different levels (cellular, molecular and genetic) with particular focus on tissue mechanical aspects, and the mini-symposium will cover a broad range of applications from orphan diseases to cancer.

Minisymposium: Exploring the tissue regeneration processes through mathematical modelling

DATA-DRIVEN MULTI-SCALE MODEL OF TISSUE REGENERATION IN AXOLOTL

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Keywords: Axolotl, Tissue regeneration, Multiscale model, Connective tissue.

In striking contrast with humans, a number of species have the ability to regenerate substantial parts of their body after tissue amputation. Among the vertebrates, the axolotl (Ambystoma mexicanum) is able to regenerate the limb and the spinal cord, among other body parts. By using a combination of mathematical modeling with imaging and cell tracking we identified key cellular mechanisms underlying spinal cord and limb regeneration in the axolotl. In this talk I will show recent results from our lab suggesting that tissue amputation initiates a regeneration program that mirrors development. To interpret these results I will discuss a multi-scale model aimed to understand the regenerative responses in the axolotl in terms of a signaling process triggering acceleration of the cell cycle and cell displacements.

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IN SILICO CLINICAL TRIALS FOR PEDIATRIC ORPHAN DISEASES: A CASE STUDY.

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Keywords: Data-driven modelling, Fracture healing, In silico models, Clinical trial.

Today over 350 million patients worldwide are affected with orphan diseases. To tackle the associated challenges, in silico models and virtual clinical trials are increasingly explored. In this study we combined mechanistic modeling with data-driven modeling in an investigative in silico clinical trial to assess the (beneficial) effect of bone morphogenetic protein (BMP) treatment on fracture healing in patients with congenital pseudarthrosis of the tibia (CPT). Although the exact etiology of CPT is still highly debated, it is hypothesized that a mutation in the Neurofibromatosis type 1 (NF1) gene results in an altered phenotype of the skeletal cells and impaired bone healing. In this study, we generated a set of 200 virtual patients from a previously established multiscale model of bone regeneration by altering the parameter values of eight key factors which describe the aberrant cellular behaviour of cells affected by NF1 mutation. Each virtual patient was simulated to receive no treatment and BMP treatment. We show that the degree of severity of CPT is significantly reduced with BMP treatment, although the effect is highly patient-specific. Moreover, machine learning techniques identified four distinct patient groups: adverse responders, non-responders, responders and asymptomatic. This study demonstrates how mechanistic and data-driven modeling are useful tools to simulate and mine data from in silico clinical trials, stratify patient populations, and improve current treatment strategies.

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WOUND EDGE FLUIDITY PROMOTES EPITHELIAL WOUND HEALING

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Keywords: Wound healing, Epithelial dynamics, Computational modelling, Image analysis.

Much work has demonstrated the importance of biochemical signalling during wound healing, however it has become clear that cells also react to mechanical stimuli. The role of mechanics during tissue repair, at the cellular level, remains poorly understood.

We are using the Drosophila wing imaginal disc as a model system to understand the mechanical basis of wound healing. We create wounds in ex vivo cultured wing discs by laser microablation and perform time-lapse imaging of wound closure. We then use automated cell segmentation and tracking software (Epitools, Heller et al., 2016) to quantify elements of wound closure, including the rate of wound closure and associated cell behaviours.

Using a combination of genetic, mechanical and computational modelling approaches, we have demonstrated that changing the mechanical properties of the tissue is sufficient to alter the rate at which wing disc wounds heal. By either increasing or decreasing the activity of Myosin II, we can respectively inhibit or promote tissue fluidity. We find that the level of tissue fluidity correlates with wound closure rate, such that wounds in the most fluid tissues close fastest. Using a computational vertex model of wound healing, we have shown that a local increase in tissue fluidity at the wound edge (rather than a global increase in tissue fluidity) leads to the greatest increase in wound closure rate. Quantification of Myosin II levels supports the notion that Myosin activity is inhibitory to tissue fluidity locally, at the wound edge.

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RECENT ADVANCES IN MATHEMATICAL MODELLING OF CELL MIGRATION

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Keywords: Cell migration, Cell motility, Viscoelastic, Bulk-surface reaction-diffusion systems, Geometric partial differential equations.

In this talk, I will review recent advances in modelling cell migration in both 2- and 3-dimensions. Advances in experimental data acquisition has given rise to a humongous amount of experimental data that is amenandable to mathematical modelling. Typical models include coupled bulk-surface reaction-diffusion systems describing the spatio-temporal dynamics of chemical species that drive cell migration. On the other hand, visco-, hyper- and poro-elastic models that describe the cellular architecture and its deformation have been developed or are in development. To couple the biochemical and biomechanical processes, geometric partial differential equations have been recently developed for the evolution of the cell surface membrane that couple the bulk dynamics to the cell surface dynamics as well as dynamics of the deformation of the environment on which the cell is migrating. In many cases, analytical solutions are not accessible and novel numerical methods have been developed to provide approximate numerical solutions of coupled bulk-surface-extracellular partial differential systems.

Cell migration is a multistep process essential for mammalian organisms and is closely linked to processes such as development, immune response, wound healing, tissue differentiation and regeneration, inflammation, tumour invasion and metastasis formation. All these processes require the orchestrated movement of cells through nonhomogeneous environments in particular directions to specific locations. Errors during this process have serious long-term health and societal consequences.