

A mathematical model with the capacity to direct and accelerate the design of cellular peripheral nerve repair conduits

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INTRODUCTION: Implantable, bioengineered tissues are increasingly showing promise as clinical solutions to traditional treatments for diseased or damaged tissue. Currently the design of such devices is driven by the outputs of experimental research, without an overarching consensus on how to combine and spatially arrange biomaterials, cells and chemical factors to achieve a defined and tissue-specific outcome. Mathematical modelling has the potential to accelerate and refine this design process, reducing financial and time costs, whilst minimizing the required number of animal-based experiments. Here we present case studies on the design of tissue-engineered constructs for peripheral nerve repair, where tissue-engineered solutions currently fall short of the gold-standard autograft.

METHODS: We present two case studies based on the following questions:

(1) How should we arrange materials within a nerve repair construct to provide sufficient mechanical guidance for directed axon growth, whilst leaving enough space for regeneration?

(2) How should we distribute cells in a construct to ensure adequate oxygenation for cellular function, whilst stimulating angiogenesis *in vivo*?

In each case study, mathematical models are presented that describe the spatial distributions of materials and factors, and the cellular response to these mechanical and chemical cues. The models rely on parameter values, which are tissue specific and quantify important behaviours (for example, the rate of metabolism of oxygen by therapeutic cells). Outputs of the mathematical models are compared against experimental data in order to inform these parameter choices and validate the model predictivity. Finally, design proposals are made for peripheral nerve repair constructs.

RESULTS: (1) The mathematical models predicts a sensitive competition between increased mechanical guidance offered by increased material content, whilst leaving sufficient space for elongating neurites to grow. Fig. 1 shows the proportion of regenerating neurites that successfully transverse a construct, as a ratio of

those generated at the proximal stump (hit ratio), for varying material content, and distance down the construct. A consistent optimum fluid volume fraction around 0.7 is identified. In a recent nerve repair experiment¹, 1500 phosphate glass fibres were arranged in a 1.8mm-diameter construct; the current analysis indicates increasing the fibre number to 3000 will improve regeneration.

(2) The mathematical model predicts oxygen, vascular growth factor and cell density levels in a construct as a function of position. Gradients in each are established due to the balance between solute diffusion and metabolism/ production, and cell proliferation and death. The model predicts the correlation between the minimum oxygen level in a construct, proportion of cell death, and production of growth factors required to induce angiogenesis and thus repair. Seeded cell distributions are presented that capitalise on this sensitive balance.

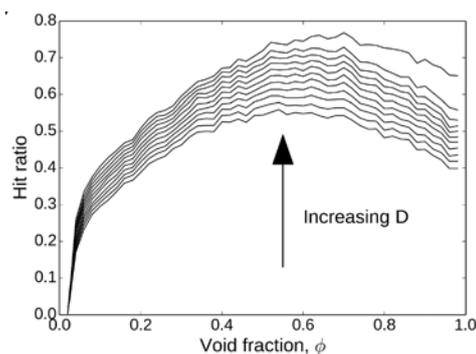


Fig. 1: Simulated hit ratios for a range of longitudinal distances down the construct, D , as a function of void fraction ϕ (volume fraction of fluid space in the construct).

DISCUSSION & CONCLUSIONS:

To develop the next generation of bioengineered tissue substitutes, it is essential to understand how to organise therapeutic cells and materials within constructs to support tissue regeneration and/ or function. Mathematical modelling has the potential to direct this design process, streamlining a field that currently relies on costly experimentation.

REFERENCES: ¹ Y.-P. Kim et al. (2012), *J Tiss Eng Reg Med* **9**(3):236-246.