A mathematical model informed by in vitro experiments to advance engineered nerve repair construct design

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INTRODUCTION: Mathematical modelling has unexploited potential as a highly cost effective and quick way of analysing and comparing the efficacy of different nerve repair construct designs prior to *in vitro* and *in vivo* experiments. Within a mathematical framework, in this case describing a cell culture well containing media and seeded collagen gel, parameter values are required to describe important attributes such as cell proliferation and VEGF release rates. In this study, data fitting against the results of corresponding *in vitro* experiments allows us to identify parameter values that were uncertain based upon the current literature. These parameters can now be used within a mathematical model describing a collagen-based engineered tissue, in order to study interactions between crucial species such as oxygen and cells, and eventually aid the design of future nerve repair constructs.

METHODS:

Differentiated adipose-derived stem cells (dASCs) were seeded in plastic compressed collagen gels at varying densities and maintained with different external oxygen levels. After 24h, viability and VEGF release was measured using CellTiter-Glo (Promega) and ELISA respectively.

A set of coupled partial differential equations was developed to describe the interactions within the *in vitro* gel between the three species of interest: cell density, oxygen concentration and VEGF concentration. The equations incorporate processes such as diffusion and cell death, alongside known parameter values from the literature [1-3]. Initial conditions representing the prescribed oxygen chamber partial pressures and initial seeded cell densities are applied. The equations were solved over a geometry representative of a cell culture well using the Multiphysics software COMSOL, and fitted to the experimental data to derive new values for uncertain parameters.

RESULTS: The approximate values of previously unknown parameters have been calculated via data fitting. Subsequent simulation results suggest that the distributions of the three species over time are, to varying degrees, sensitive to key parameters within the model.

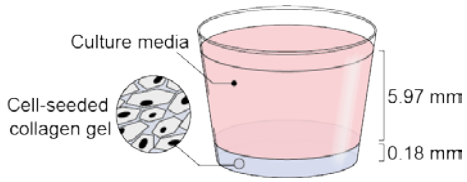

Fig. 1: In vitro experimental setup.

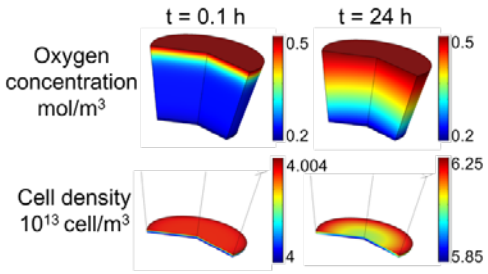

Fig. 2: Simulated oxygen concentration and cell density distributions across cell culture well, at times t = 0.1h and t = 24h.

DISCUSSION & CONCLUSIONS: The *in vitro* simulation results highlight the need to properly consider properties such as seeded cell density when designing engineered tissue, due to the impact that changing distributions of species can have upon processes that are key to clinical efficacy, such as angiogenesis and neuronal growth in this context. Values of the parameters obtained using data fitting can now be used to complete simulations of species within different *in vivo* nerve repair construct designs.

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