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Mathematical modelling of oxygen, glucose and lactic acid reaction kinetics for osteoblasts and mesenchymal stem cells

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INTRODUCTION: Osteoporosis causes 8.9 million fragile fractures a year worldwide[1], which often result in non-unions and require either autologous or allogeneic grafting. Complications associated with these procedures, such as morbidity of the donor site and rejection of the implant[2], drive bone tissue engineering. Protocols for dynamic, 3D cell cultures, able to produce viable and sufficiently large tissue constructs, are investigated. Mathematical modelling is a useful tool in this process, highlighting the balance of chemical (nutrients) and mechanical (shear force) factors in the cell culture environment.

METHODS: One potential strategy for producing human-like bone tissue is using bioglass microspheres as scaffolds for MG63 osteoblasts and mesenchymal stem cells (MSCs), which are then allowed to self-assemble. Modelling is used to propose a suitable scaling-up approach. The work here focuses on cellular metabolism in the initial stages of the set-up, under diffusive only transport.

The reaction equations for oxygen and glucose uptake are based on Michaelis-Menten kinetics[3]:

$$R_i = \phi\, c_i\, V_{max}/(P_{50} + c_i) \qquad (1)$$

where R_i *[mol/s.m^2]* is the consumption rate of the chosen nutrient, c_i *[mol/m^3]* is its concentration, ϕ *[cells/m^2]* is the cell density, V_{max} *[mol/s.cell]* is the maximum rate of consumption and P_{50} *[mol/m^3]* is the concentration at which the consumption rate is 50% of V_{max}.

The level of aerobic oxidation of glucose also determines the amount of lactic acid produced by anaerobic fermentation of glucose due to oxygen deficiency[4]. This relationship can be described by:

$$R_l = -2(R_g - R_c/6) \qquad (2)$$

The model was solved in COMSOL Multiphysics. The geometry of a well from a 96-well plate (Corning) was used. Initial conditions reflecting oxygen saturation of the media, glucose concentration of 1 g/l and no lactic acid, were chosen. A constant concentration was assumed at the top boundary of the well due to oxygen diffusion from air. The cells were modelled as an infinitely thin layer on the bottom of the well, with consumption or production of the relevant species represented as flux loss/gain boundary conditions.

RESULTS: Cell-type specific coefficients need to be generated for a predictive model. A sensitivity analysis was used to characterise their behaviour. Values for V_{max} and P_{50} were obtained from literature, and the smallest and largest values used to create a range for testing. Changes in V_{max} result in greater variation in the concentration than those in P_{50} (Fig.1). In the case of oxygen, for a range encompassing one order of magnitude for both coefficients, the parameter sweep of V_{max} caused a 57 times bigger difference between the minimum and maximum oxygen concentration compared to P_{50}.

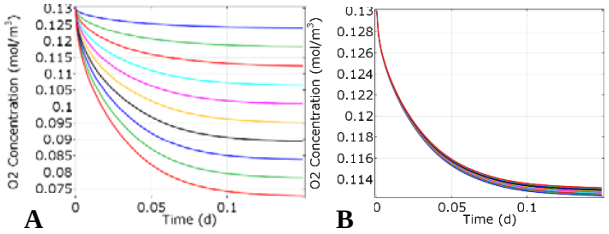

Fig. 1: Different oxygen concentrations for A) V_{max} from 9×10^{-18} to 9×10^{-17} mol/s.cell and B) P_{50} from 7×10^{-4} to 9×10^{-3} mol/m^3.

DISCUSSION & CONCLUSIONS: This analysis suggests that the next step in improving the model is to data fit V_{max} with the experimental results. This would pave the way to establishing a relationship between cell number, metabolic activity and ultimately, flow sheer stress.

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