EFFECTS OF ELASTICITY ON CELL GROWTH IN A TISSUE-ENGINEERING SCAFFOLD PORE

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Introduction

Severe injury and disease have devastating effects, such as loss of organ function due to irreversible tissue damage leading to diminished quality of life. While surgical techniques may recover partial function via organ transplantation, it has limitations, such as organ rejection, infection, shortage of viable organs for transplantation and costs. The burden of disease and injury encourages the pursuit of alternative solutions. Tissue engineering techniques address limitations associated with current practices. The goal of in vitro tissue engineering involves the fabrication of bio-compatible scaffolds to provide structure and support to cells and facilitate cell growth for restoration of damaged or diseased tissues. Mathematical modeling eliminates trial and error, minimizes experimental cost, identifies initial construct geometries for optimizing growth of target cells and provides a basis for the design of scaffolds. The focus of this research centers on predicting cellular proliferation rates in an elastic scaffold by mathematical modeling to determine the influence and specific mechanisms which scaffold properties and microenvironment have on cell proliferation.

Mathematical Modeling

We consider a simple continuum model, in which the scaffold consists of a series of identical nearly cylindrical pores spanning the entire scaffold, with depth-dependent radius. Therefore, we focus on a single scaffold pore, with cells initially lined on the pore wall, while nutrient solution flows through the pore as shown in Fig. 1. The pore wall is seeded with a layer of cells, which have negligible initial thickness. L and R denote the length and radius of the pore, respectively. The pore aspect ratio ϵ is defined as $\epsilon = R/L \ll 1$. We assume that the concentration of nutrient supplied to the cells are held at constant Q_i, therefore the applied pressure at the pore inlet p, continuously increases.

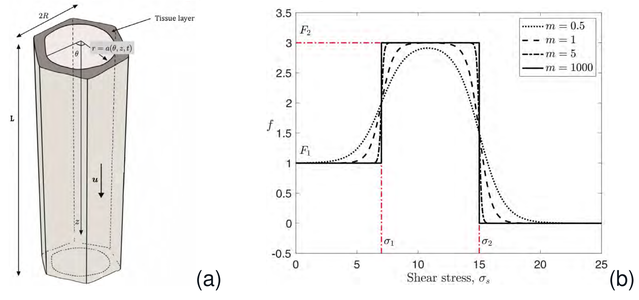

Fig. 1: (a) Schematic diagram of a tissue-lined pore within a tissue engineering construct. (b) Growth function $f(x) = F_1 + (F_2 - F_1)\left[\frac{1+\tanh(m(x-\sigma_1))}{2}\right] - F_2\left[\frac{1+\tanh(m(x-\sigma_2))}{2}\right]$ appears in (3).

The geometry of the problem requires us to work in cylindrical coordinates (r, θ, z), where z is aligned with the pore axis, such that the cell layer lining the interior pore wall is described by $a(\theta, z, t) = a_0(t) + \epsilon\left(\Lambda(z,t)\cos n\theta + \Upsilon(z,t)\right) + \mathcal{O}(\epsilon^2)$, where $\Lambda(z,t)$ and $\Upsilon(z,t)$ are functions to be pinned down and n is an integer that describes the number of lobes in the geometry of the underlying substrate.

Governing Equations

Fluid Dynamics: Nutrient solution is considered to be an incompressible Newtonian fluid, with viscosity μ and density ρ. The nutrient flow of velocity $\boldsymbol{u}$ is subject to no slip and no penetration boundary conditions, and is governed by the Stokes equations,

$$\boldsymbol{\nabla} p = \mu \nabla^2 \boldsymbol{u}, \quad \boldsymbol{\nabla} \cdot \boldsymbol{u} = 0. \tag{1}$$

Elasticity: Elasticity affects the degree of pore wall deformation under fluid pressure forces. The elastic pore expands as pressure increases and the deformation of pore is described by Navier-Cauchy equations,

$$\frac{\partial^2 \Omega}{\partial T^2} = \nabla^2 \boldsymbol{\Omega} + \frac{1}{(1-2\nu)} \boldsymbol{\nabla}(\boldsymbol{\nabla} \cdot \boldsymbol{\Omega}), \tag{2}$$

where $\boldsymbol{\Omega} = (\Omega_r, \Omega_\theta, \Omega_z)$ is the pore wall displacement, ρ_m is the scaffold pore density, E and ν are the Young's Modulus and Poisson's ratio of the scaffold, respectively. We assume that the nutrients flow through the pore over a much shorter time scale compared to that of the pore wall deformation due to elasticity, therefore, we impose an elasto-static condition onto (2), i.e., $\frac{\partial^2 \Omega}{\partial T^2} = 0$.

Cell Growth: The pore radius shrinks as cell growth increases for rigid scaffolds, and cell proliferation occurs rapidly when exposed to intermediate levels of shear stress, and in regions with higher curvature [1, 2, 3]. The growth of cells is given by

$$\frac{\partial a}{\partial t} = -\lambda \kappa f(\sigma_s). \tag{3}$$

Here, λ is the characteristic growth rate ($\mathrm{m^2 s^{-1}}$), $\kappa = \boldsymbol{\nabla} \cdot \boldsymbol{n}$ is the mean curvature and function f captures the total shear stress σ_s on cell growth (see Fig. 1 (b)).

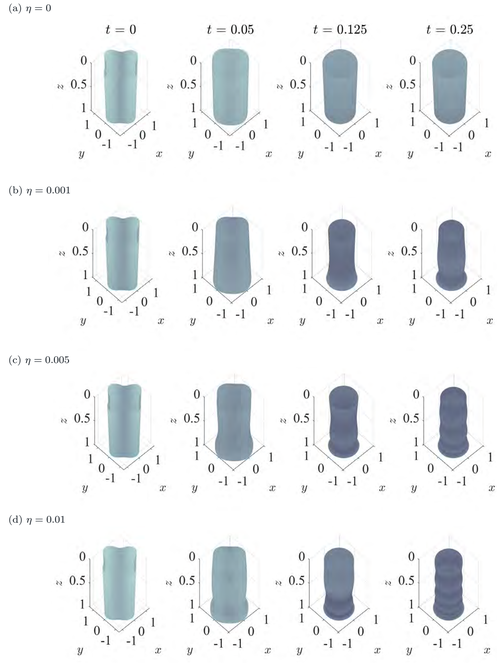

Fig. 2: Three-Dimensional evolution of scaffold pore for several values of dimensionless elastic compliance η.

Results

According to Fig. 1(b) and (3), the cell growth is low, enhanced and zero when the total shear stress at the channel wall, exerted by the nutrient flow, is low, moderate and high, respectively. The expansion of the elastic pore under constant flux of nutrient flow facilitates cell growth by lowering the shear stress on the cell to intermediate values. The 3D evolution of the scaffold channel is shown in Fig. 2 for different values of scaffold elasticity over time. Figure 2(a) illustrates the change in configuration for non-elastic scaffolds, where expansion is not possible. The channel continually shrinks before settling into a steady-state phase. Figures 2(b)-2(d) depict instances where the dimensionless scaffold elasticity compliance η increases.

Scaffold pore design: A major point of interest to manufacturers involves the development of scaffolds which facilitate optimal cell growth. Determining which initial pore configuration facilitates optimal cell growth requires reversing the simulation for total cell growth in time from initial to final times. Figure 3 shows the channel configurations at initial times as scaffold elasticity compliance increases. These results indicate increasing material elasticity results in a funnel shape for the optimal initial pore geometry.

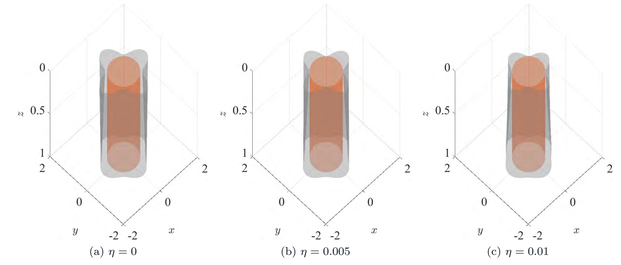

Fig. 3: Surface plots for the scaffold design with uniform final radius.

Conclusion

We have presented a mathematical model for cell growth within an elastic tissue engineered scaffold pore. The flow of nutrient to the cells is governed by the Stokes equations, and the effects of elasticity by Navier-Cauchy equations, while the cell proliferation is captured via a growth law which incorporates the effects of pore morphology on the cell growth. The inclusion of time-reversal techniques into the analysis of our mathematical model offers a comprehensive method to obtain predictable, reproducible results to obtain optimal scaffold geometry.

References

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