**Assignment 8: Cell and Tissue Mechanics**

**EN 585.729 Cell and Tissue Engineering**

**Problems**

1. The Hagen-Poiseuille equation describes flow through a cylindrical tube. We discussed this in the context of blood flow but it is also applicable to respiration where air flows through cylindrical alveoli. Please use this equation to explain why breathing is so difficult for someone suffering from just mild asthma.

In a person with asthma, the airways (trachea, bronchi, bronchioles) are inflamed with a secretion of excessive thick mucus which lines up these airways. This leads to a decrease of the diameter of these airways available for air flow. In the airways, the flow of air could be considered laminar and incompressible (Reynolds number is 2,084 in the trachea to drop to 0.01 in bronchioles and alveoli [1]). Even if assumptions of the Hagen-Poiseuille equation are not strictly verified for the respiratory tract; it shows that resistance to the air is inversely proportional to fourth power of the radius:

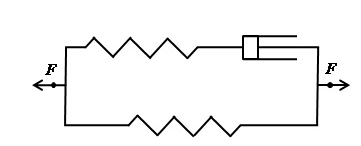
R = (8 x η x L) / (π x R4)

η: viscosity, L: length of the cylinder, R: radius

Therefore a small decrease in the radius of the airways causes a large increase in the airway resistance, decreasing significantly the amount of oxygen a person with asthma can inspire which explains the difficulty of these people to breath during an asthma period.

1. Derive the ordinary differential equation for the Kelvin viscoelastic solid (pictured below). Show **all of your work** (each step!) for full credit.

**x**



**k2**

**x2**

**x1**

**k1**

**η**

**x**

We have:

F1 = k1 x1 = η dx2/dt

F2 = k2 x

Ftot = F1 + F2

Taking the derivative on both sides

dFtot /dt = dF1/dt + dF2/dt

= k1 dx1/dt + k2 dx/dt

x = x1 +x2, thus x1 = x - x2 and dx1/dt = dx/dt - dx2/dt, substituting in the last equation gives:

dFtot /dt = k1 (dx/dt - dx2/dt) + k2 dx/dt

= (k1 + k2) dx/dt - k1 dx2/dt

From F1 = η dx2/dt and Ftot = F1 + F2

dFtot/dt = (k1 + k2) dx/dt - k1 (F1/η)

= (k1 + k2) dx/dt - k1/η (Ftot - F2)

Rearranging the terms:

dFtot/dt + k1/η Ftot = (k1 + k2) dx/dt + k1/η F2

dFtot/dt + k1/η Ftot = (k1 + k2) dx/dt + k1 k2/η x

The final ODE is:

**Ftot + (η/k1)dFtot/dt = η (k1 + k2)/k1 dx/dt + k2 x**

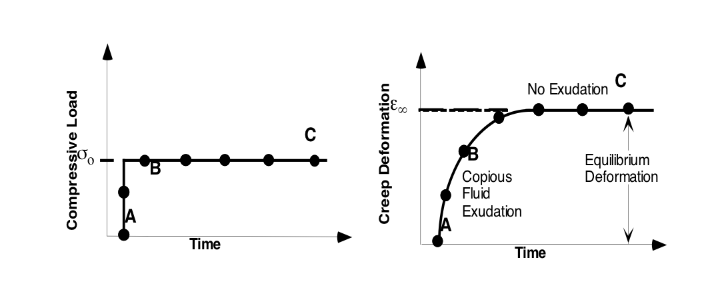
Finally, 2 F = **Ftot** and replacing in the previous equation:

**F + (η/k1)dF/dt = η (k1 + k2)/(2 k1) dx/dt + k2/2 x**

1. In lecture we discussed the biomechanics of articular cartilage and how important it is for tissue engineers to understand these mechanics in order to design successful tissue substitutes.
   1. Based on the shape of the confined compressive load test on cartilage what type of model would you use to describe it mechanically and why?

The confined compressive load test applies a constant compressed load σ0, it’s a one-time action which could be represented by the step function shown on the graph on the left. This step function is similar to the load vs. time of the Spring model. Once released, the compressive load applied goes back immediately to 0.

b. What components (dashpots and springs...) describe the behavior shown below on the right? What phase(s) of cartilage are represented by the component(s)?



The behavior shown on the right is the creep vs. time of the Voigt model. Initially the creep deformation is relatively rapid, and corresponds to a large fluid exudation. This part of the graph characterizes the fluid phase of the cartilage. As the creep deformation slows down and approaches a constant value, the fluid flow slows similarly. At equilibrium, the creep deformation is constant and the fluid flow has stopped; characteristic of the solid phase of the cartilage.

4. Over the last two weeks you’ve read on the use of microscale topographies (Nikkhah et al. Engineering microtopographies to control the cell-substrate interface). In 300 words or less please explain how microtopographies can be employed in the development of engineered tissues. What tissue properties can they influence? What cell behaviors can they control?

Mechanobiology, through the mechanical cues provided by cell-substratum and cell-cell contacts expressed in the form of shear stress, hydrostatic pressure, stiffness, or intercellular tugging, affects cellular proliferation, migration, and stem cell differentiation.

Microtopographies have been used to study, understand and recreate these cues:

* Studies have demonstrated that geometries of the microstructures on the substrate like pillars [2], wells [3], pits [4], pyramidal shapes [5], curved surfaces [6]; including height and width can influence cell alignment, their morphologies and polarities [7].
* Cell migration direction and velocity can be regulated by microscale topographies. Average migration speed is higher on microgrooved substrates than on flat surfaces [8,9,10,11]. In vitro, stiffness of the substrate can also guide cell migration (durotaxis) [12].
* Substrates with different patterns have provided physical stimulation for systematic differentiation of stem cells. In a study, neural stem cell (NSCs) cultured on chitosan films differentiated into astrocytes [13].

For neural tissue engineering, combination of uniquely designed micro grooves or pillars with molecules such as laminin [14] or nerve growth factors secreting astrocytes [15], or Schwan cells [16], have induced neurite alignment, extension, growth and differentiation. This research is particularly important for spinal cord injuries (SCIs) therapies to promote nerve regeneration. Multichannel conduits with seeded Schwann cells have mediated greater nerve regeneration and shortened the time for recovery in rats with transected spinal cord or sciatic nerves [17,18].

Engineered cardiac tissue have been able to recreate the anisotropy and mechanical properties of the myocardium; with an increase on cardiomyocytes systolic intracellular Ca2+ and slower diastolic rise in calcium [19].

In bone and cartilage tissue engineering, significant progresses have been made. Kirmizidis et al. [20], were able to align osteoblasts by varying the width of the grooves. Critical for cartilage repair, Moutos et al. [21], induced uniform spreading of chondrocytes with rounded morphologies.

**Sources:**

[1]: Chiu-sen Wang – Inhaled particles – Interface Science and Technology. Volume 5C - Elsevier 2005 page 31-54.

[2] Kolind K, Dolatshahi-Pirouz A, Lovmand J, Pedersen FS, Foss M, Besenbacher F. A combinatorial screening of human fibroblast responses on micro-structured surfaces. Biomaterials 2010;31:9182-91.

[3] Wang L, Murthy SK, Fowle WH, Barabino GA, Carrier RL. Influence of microwell biomimetic topography on intestinal epithelial Caco-2 cell phenotype. Biomaterials 2009;30:6825-34.

[4] Wan YQ, Wang Y, Liu ZM, Qu X, Han BX, Bei JZ, et al. Adhesion and proliferation of OCT-1 osteoblast-like cells on micro- and nano-scale topography structured pply(L-lactide). Biomaterials 2005;26:4453-9.

[5] Le Saux G, Magenau A, Boecking T, Gaus K, Gooding JJ. The relative importance of topography and RGD ligand density for endothelial cell adhesion. Plos One 2011;6:e21869.

[6] Nikkhah M, Strobl JS, Agah M. Attachment and response of human fibroblast and breast cancer cells to three dimensional silicon microstructures of different geometries. Biomed Microdevices 2009;11:429-41.

[7] Gomez N, Chen S, Schmidt CE. Polarization of hippocampal neurons with competitive surface stimuli: contact guidance cues are preferred over chemical ligands. J R Soc Interface 2007;4:223-33.

[8] Kaiser J-P, Reinmann A, Bruinink A. The effect of topographic characteristics on cell migration velocity. Biomaterials 2006;27:5230-41.

[9] Kim D-H, Han K, Gupta K, Kwon KW, Suh K-Y, Levchenko A. Mechanosensitivity of fibroblast cell shape and movement to anisotropic substratum topography gradients. Biomaterials 2009;30:5433-44.

[10] Dalton BA, Walboomers XF, Dziegielewski M, Evans MDM, Taylor S, Jansen JA, et al. Modulation of epithelial tissue and cell migration by microgrooves. J Biomed Mater Res 2001;56:195-207.

[11] Li S, Bhatia S, Hu YL, Shin YT, Li YS, Usami S, et al. Effects of morphological patterning on endothelial cell migration. Biorheology 2001;38:101-8.

[12] Lo C-M, Wang H-B, Dembo M, Wang Y-l. Cell movement is guided by the rigidity of the substrate. Biophys J 2000;79:144-52.

[13] Wang G, Ao Q, Gong K, Wang A, Zheng L, Gong Y, et al. The effect of topology of chitosan biomaterials on the differentiation and proliferation of neural stem cells. Acta Biomater 2010;6:3630-9.

[14]: Gomez N, Lu Y, Chen S, Schmidt CE. Immobilized nerve growth factor and microtopography have distinct effects on polarization versus axon elongation in hippocampal cells in culture. Biomaterials 2007;28:271-84.

[15] Recknor JB, Sakaguchi DS, Mallapragada SK. Directed growth and selective differentiation of neural progenitor cells on micropatterned polymer substrates. Biomaterials 2006;27:4098e108.

[16] Lietz M, Dreesmann L, Hoss M, Oberhoffner S, Schlosshauer B. Neuro tissue engineering of glial nerve guides and the impact of different cell types. Biomaterials 2006;27:1425-36.s

[17] Krych AJ, Rooney GE, Chen B, Schermerhorn TC, Ameenuddin S, Gross L, et al. Relationship between scaffold channel diameter and number of regenerating axons in the transected rat spinal cord. Acta Biomater 2009;5:2551-9.

[18] Rutkowski GE, Miller CA, Jeftinija S, Mallapragada SK. Synergistic effects of micropatterned biodegradable conduits and Schwann cells on sciatic nerve regeneration. J Neural Eng 2004;1:151-7.

[19] Yin L, Bien H, Entcheva E. Scaffold topography alters intracellular calcium dynamics in cultured cardiomyocyte networks. Am J Physiol Heart Circ Physiol 2004;287:H1276-85.

[20] Kirmizidis G, Birch MA. Microfabricated grooved substrates influence cellcell communication and osteoblast differentiation in vitro. Tissue Eng Part A 2009;15:1427-36.

[21] Moutos FT, Freed LE, Guilak F. A biomimetic three-dimensional woven composite scaffold for functional tissue engineering of cartilage. Nat Mater 2007;6: 162-7.