Evaluation of the Physical Impact of Implant Micromotion on the Cellular Environment of the Soft Tissue-Biomaterial Interface

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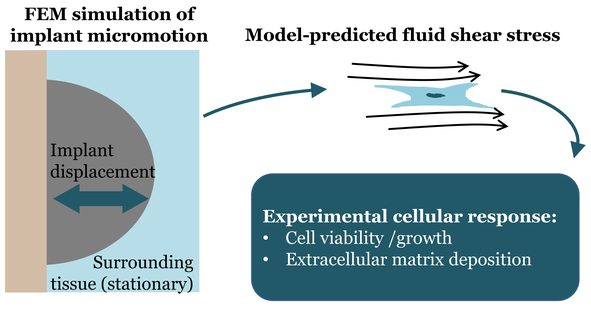
Abstract

Soft tissue implants are associated with numerous complications involving a chronic inflammatory, tissue remodeling response. For example, FDA has been aware of a potential correlative link between textured breast implants and incidence of breast implant associated-anaplastic large cell lymphoma (BIA-ALCL) in women who received breast augmentation or reconstructive surgery. This link, associated with the geometric aspect of the implant, suggests physical interactions between soft tissue implants and host tissues may contribute to pathogenesis in tissues, such as breast tissue. By increasing implant contact area with host tissues, surface texturing promotes tissue ingrowth, which influences implant micromotion. The unique micromotion pattern of textured soft tissue implants may introduce a mechanical force environment for the immune cells at the tissue-implant interface that promotes inflammation. The purpose of this study is to (1) build finite element models of several types of soft tissue-implant interfaces to predict micromotion-induced fluid shear stresses at the cellular scale, and (2) utilize in vitro culture models and biological assays (cytotoxicity, protein synthesis, collagen formation, etc.) to evaluate the toxicity of the predicted fluid shear stress distributions. The finite element models, developed on COMSOL, were designed to be representative of an implant-poroelastic soft tissue interface characterized by two types of geometries (textured and smooth), three levels of tissue integration (0%, 50%, and 100%), and micromotion displacement functions. The predicted shear stress generated in the surrounding model soft tissues were then used as a basis for microfluidics-based cell culture studies to evaluate their impact on the biological responses of fibroblasts, which were selected as a model cell type present at the tissue-implant interface. The current COMSOL model predicted that cells in a model soft tissue-implant interface under the conditions evaluated could be exposed to oscillatory shear stresses as high as 150 dyne/cm². Currently, we are continuing to refine our computational model as well as conduct our microfluidic cell studies. We expect to elucidate key information that may be used to help develop new assessment approaches to help with the regulatory review of textured soft tissue implants.

Introduction

This study aims to (1) develop a finite element model that predicts implant micromotion-induced fluid shear stress in surrounding tissues, and (2) characterize the response of cells to these stresses in terms of cell health and extracellular matrix remodeling.



Materials and Methods

Finite element model (FEM) analysis – The impact of implant micromotion on the surrounding tissue environment was evaluated using a model soft tissue-implant interfacial geometry [1], varying degrees of surface texture and tissue integration (**Figure 1**), and a sinusoidal displacement function to describe the movement of the implant surface relative to the surrounding tissue (**Figure 2**).

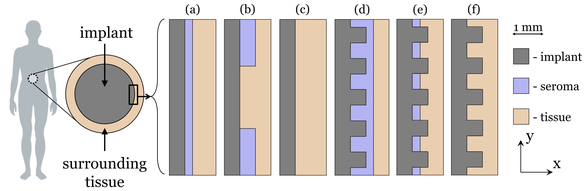


Figure 1. Model description and geometry. Smooth, (a-c) and textured (d-f) implant surfaces with 0% (a, d), 50% (b, e), and 100% (c, f) tissue integration—i.e. percent of tissue adhered directly to the implant.

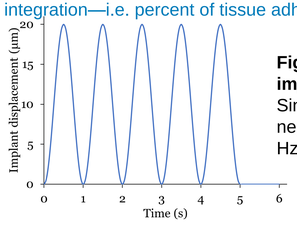


Figure 2. Displacement, $\vec{s}$, of the implant relative to the tissue. Sinusoidal displacement is applied in the negative with an amplitude of 20 um at 1 Hz as follows:

$$\vec{s} = 20(\sin(2\pi t + \pi/2) - 1)$$

Fibroblast fluid shear stress response – Human Dermal Fibroblast (HDF) populations were exposed to oscillatory fluid shear stresses based on FEM analyses using a fluid flow culture system (Ibidi) capable of exposing cells to a maximum of 80 dyne/cm² for 6-72 hours. The cytotoxicity and protein expression activity of these cells were assessed (**Figure 3**).

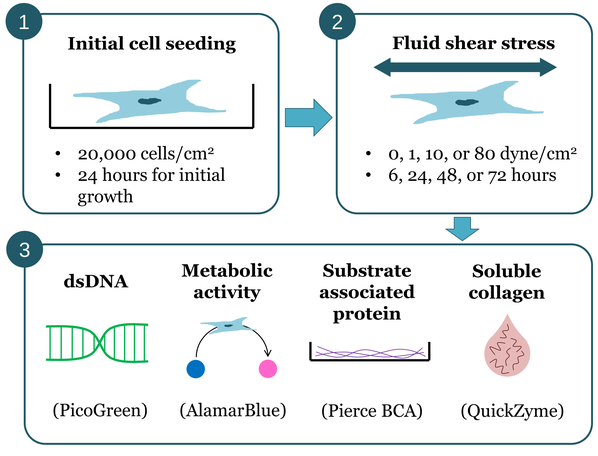


Figure 3. Experimental methods. Cells were cultured in microfluidics slides for 24 hours prior to shear stress exposure. Cell viability / growth were assessed using DNA staining and AlamarBlue assays. Extracellular matrix deposition was assessed by measuring protein deposition on cell substrates (substrate associated proteins) and collagen release into supernatants.

Results and Discussion

FEM shear stress predictions – The finite element model predicted shear stresses up to 150 dyne/cm² at 1 Hz (**Figures 4 and 5**). Shear stress amplitudes depended on degree of implant texture and tissue integration.

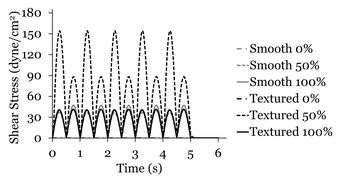


Figure 4. Shear Stresses generated at the tissue interface between smooth versus textured surfaces. Maximum stress occurs in the 50% textured case.

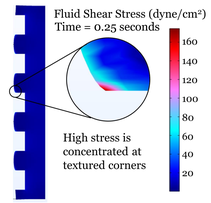


Figure 5. Fluid shear stress distribution for textured surface with 50% tissue integration. The highest stresses occur at the corners of the surface texture.

Cellular viability and activity – Cell viability (**Figure 6**) and protein deposition on substrates (**Figure 7**), but not collagen release into supernatants (**Figure 8**), appears to depend on the amplitude and/or duration of shear stress exposure.

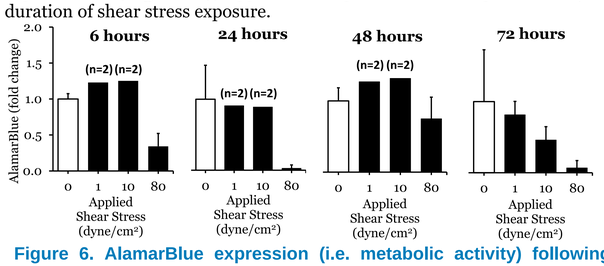


Figure 6. AlamarBlue expression (i.e. metabolic activity) following fluid shear stress exposure for denoted times. Bars are mean AlamarBlue expression relative to cells cultured under no-flow conditions (white bars) but otherwise similar experimental conditions (n = 3 unless otherwise specified), error bars represent standard deviation.

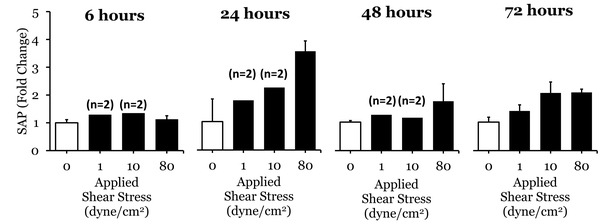


Figure 7. Fold-change in substrate-associated protein for each group following fluid shear stress exposure for denoted times. Bars are mean SAP levels relative to cells cultured under no-flow conditions (white bars) but otherwise similar experimental conditions (n = 3 unless otherwise specified), error bars represent standard deviation.

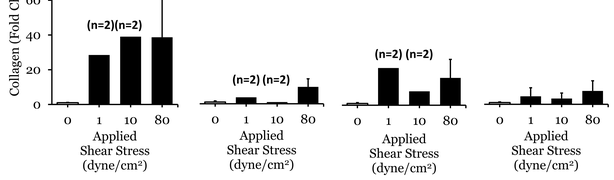


Figure 8. Fold-change in soluble collagen for each group following fluid shear stress exposure for denoted times. Bars are mean collagen levels relative to cells cultured under no-flow conditions (white bars) but otherwise similar experimental conditions (n = 3 unless otherwise specified), error bars represent standard deviation.

Summary / Concluding Remarks

- ❑ FEM analyses predicts
  - micromotion-induced generation of interstitial fluid shear stresses in the tissue-implant interface can reach as high as 150 dyne/cm²; and
  - the highest shear stress amplitudes are associated with tissue-implant interfaces associated of textured implants with 50% tissue integration
- ❑ Cell culture studies demonstrate that fibroblasts exposed to shear stress regimes predicted to occur at the tissue-implant interface exhibit changes in cell viability/activity that depends on the amplitude of the applied stimulus
- ❑ Data collected in this study will be used to establish a mechanotoxicity-implant approach or tool to assess cellular response to implant surfaces.
- ❑ Future work includes
  - Evaluate cellular responses to exposure to additional shear stresses at additional time points to refine the mechanotoxicity model under development
  - Assess additional responses of cells to the shear stress regimes predicted to be generated at a tissue-implant interface undergoing micromotion.

ACKNOWLEDGEMENTS: This work was supported by a grant from Office of Women's Health of the United States Food and Drug Administration (FDA; Department of Health and Human Services) and partially administered by the Oak Ridge Institute for Science and Education through an agreement between the U.S. Department of Energy and FDA.

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REFERENCE: [1] Hung, Ben P., et al. "Putative mechanobiological impact of surface texture on cell activity around soft-tissue implants undergoing micromotion." Biomechanics and Modeling in Mechanobiology 21.4 (2022): 1117-1131.