MECHANICS OF CELL SPHEROIDS UNDER LARGE DEFORMATIONS

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Introduction

Fibrosis, the excessive accumulation of extracellular matrix (ECM) by activated fibroblasts, is a common feature of different pathological conditions. Fibroblasts are mechanosensitive cells and increased stiffness of the ECM can activate fibrotic pathways [1]. To study the mechanical properties of the ECM *in vitro*, fibroblasts are cultured in 3D spheroids. Mechanical assessment of cell spheroids can be accomplished via parallel plate compression. Mechanical properties of cell spheroids are determined from force *vs* displacement (F-δ) curves but available methods for extracting material properties are limited. Many approaches rely on applying (extended) Hertzian theory to the loading part of F-δ curves to fit for a compression modulus [2]. As spheroids exhibit low stiffness, they undergo large deformations at small external forces, and current contact mechanics models fail to describe such deformation behavior [3,4]. Here, we present a model including large deformation formulation, based on a hyperelastic material law to describe the deformation of cell spheroids subjected to parallel-plate compression.

Methods

Cell spheroids consisting of primary human fibroblasts cultured for four days were subjected to parallel-plate compression testing (MicroSquisher, CellScale) fitted with a round tungsten cantilever and accompanying SquisherJoy V5.23 software (CellScale, Ontario, Canada). The fluid bath test chamber was filled with sterile phosphate buffered saline (pH=7.4), and stage and optics were calibrated according to manufacturer's instructions. Samples were compressed up to 50% apparent linear strain at different displacement rates. F–δ data was fitted using linear least squares regression on the Hertz and Tatara [3] models (custom MATLAB code) with fully constrained contact points (F =0, δ =0). Image analysis was performed to determine contact radius and lateral expansion of cell spheroids under compression.

Results

The dependence of compression modulus on the displacement rate is illustrated in Figure 1a. Furthermore, the hysteresis between the approach and retraction curves indicates viscous behavior of cell spheroids. Hertzian theory can be applied for compressive displacements up to 10-25% (depending on displacement rate). For larger deformations, where the force follows the third and fifth power of the displacement, Tatara analysis was used to extract the compression modulus (Figure 1b). The predicted contact radius and lateral expansion of cell spheroids were found to be in good agreement with the data obtained from image analysis. However, the error was significant in the case of larger deformations. Beyond 40% apparent linear strain, the volume of the cell spheroids decreased (compressible material) due to poroelasticity.

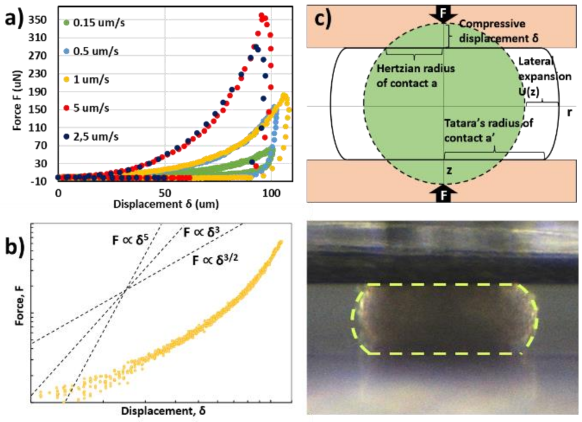

Figure 1: a) F-δ curves at different displacement rates. b) F-δ illustrating the transition from Hertzian behavior at small displacements to approximately P∝5 at large deformations. c) Shape profile of cell spheroid before and after compression.

Discussion

The Hertzian theory and its modifications can be applied for small deformations while, for larger deformations, the Tatara numerical analysis is able to describe the deformation behavior of cell spheroids providing also their lateral profile. This indicates that linear elastic continuum mechanics with some important modifications can be applied to the case of large deformations. Nevertheless, spheroids exhibit at least also viscous behavior, which should be added in future models.

References

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Acknowledgements

Authors acknowledge funding from Marie Skłodowska-Curie COFUND program under the EU Horizon 2020 research and innovation programme and from an International Mobility grant of the Autonomous Province of Bolzano.