Theoretical modeling of single- and multi-cell *mechanotropism*

Stefania Palumbo[1,2], Arsenio Cutolo[1,2], Angelo R. Carotenuto[1,2], Massimiliano Fraldi[1,2]
[1]Department of Structures for Engineering and Architecture (DIST), University of Napoli "Federico II", Napoli, Italy
[2]Laboratory of Integrated Mechanics and Imaging for Testing and Simulations (LIMITS), University of Napoli "Federico II", Napoli, Italy
Email: stefania.palumbo@unina.it

Summary

Cells continuously interact with the environment through biochemical and mechanical signals, thus dynamically tuning their behavior, including motion and organization. In particular, *mechanotropism* -the substrate-mediated cell reorientation in response to mechanical forces- plays a crucial role in driving self-arrangement of cells during tissue morphogenesis and remodeling. With this in mind, the present study introduces a theoretical model aimed at predicting optimal cell reconfigurations originating from elastic interactions with the substrate. By describing cells as force-dipoles and applying elasticity theory, we analyze how external forces influence single-cell polarization and how cell-cell mechanical sensing guides collective rearrangement. Our results retrace behaviors observed for cell cultures *in vitro*, such as strain-driven alignment and multicellular network formation, with novel insights into the role of Poisson ratio and auxeticity of the substrate. This research provides new knowledge into the cell mechanobiological behavior and lies the foundation for designing innovative engineered scaffolds for biomedical applications.

Introduction

Along with biochemical signals, adherent cells communicate via mechanical fields, actively generating stresses that deform the substrate and sensing surrounding material properties and strains through force transmission at focal adhesions [1]. Despite advances in understanding mechanotransduction, how mechanical cues guide single-cell motion and collective dynamics remains still partially unclear. Therefore, starting from experimental evidences from the literature [2,3], showing cells realigning under the effect of both external forces prescribed on the substrate and elastic interactions among neighboring cells, this study explores cell *mechanotropism* by means of a theoretical modeling approach.

Methods

By taking into account experimental data from the literature, cells are here modelled as force-dipoles transferring contractile forces to the substrate, the latter being described as a homogeneous and isotropic elastic half-space. Linear elasticity solutions are hence employed, together with a biophysically consistent principle of energy minimization, to predict cell reorientation dynamics and optimal equilibrium configurations.

Results and Discussion

Under the action of fences of exogenous point-forces prescribed on the substrate, a multiplicity of non-trivial optimal cell polarizations is determined as depending on the distribution, magnitude and distance of the loads with respect to a stationary (i.e. non-migrating) adherent cell. On the other hand, the collective self-arrangement of non-confluent cell populations emerges as the non-cooperative response of a nonlinear dynamical system with degrees of freedom provided by the orientations of multiple cells. Specifically, our model successfully reproduces observed cellular behaviors, such as the single-cell alignment along strain-oriented directions and the formation of multiple cell strings and networks [3]. Notably, auxetic substrates, i.e. substrate with negative Poisson's ratio, lead to find unprecedented orientation patterns.

Conclusions

Our study highlights the role of substrate-mediated interactions in regulating single-cell reorientation and collective cell dynamics, offering new insights into the development and repair of structured, functional tissues. These findings might contribute to the design of advanced scaffolds for biomedical applications.

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