Designação do Projeto|	Cell2Tissue .: Matéria Ativa em Substratos: das células aos tecidos
Código do Projeto|	LISBOA-01-0145-FEDER-028146
Objetivo Principal|	Reforçar a Investigação, o desenvolvimento tecnológico e a inovação
Região de Intervenção|	Lisboa
Entidade Beneficiária|	FCiências.ID – Associação para a Investigação e Desenvolvimento de Ciências
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Objetivos

We aim at a fundamental understanding of the swarm behavior of unicellular organisms and cell proliferation on substrates. The physics of cells on substrates is a multiscale problem. At the cell scale: biochemical/biomechanical processes in the interior and surroundings of the cell control the dynamics. As they move around, proliferate, or adhere to other cells, they adjust their shape to the external constraints. The mechanical stresses resulting from the cell-cell and cell-substrate interactions trigger mesoscopic collective rearrangements that affect the morphology and mechanical properties of the tissue. Despite this complexity, relevant mechanisms can be isolated to develop models of practical interest.

Atividades

We contributed to the fundamental understanding of the collective dynamics of active particles on substrates, from single cells to confluent tissues.

Interfacial properties of active matter (T1 and T2):
A rejection-free Kinetic Monte Carlo (KMC) approach was developed, which predicts a motility-induced phase separation of purely repulsive active particles, and the bulk coexistence of dense liquid-like and dilute vapour-like steady states. We proposed an "ensemble", with a varying number of particles, analogous to a grand canonical ensemble in equilibrium, to investigate the wetting of a solid–vapour interface by the liquid "phase". Our results suggest that the complete wetting scenario persists in the whole range of activities considered. To account for hydrodynamic effects, we developed a hybrid method of lattice Boltzmann with a multi-relaxation-time collision operator and finite differences to model the interface between nematic and isotropic phases of active liquid crystals. We showed that the interface in a channel is stable over a range of temperatures around the passive coexistence and disappears when one of the two phases becomes unstable. Motivated by experimental results for the propagation of active–passive interfaces of bacterial Serratia marcescens swarms, we characterized the active nematic phase of the model through the calculation of the spatial and temporal auto correlation functions and the energy spectrum and discussed its description of the statistical dynamics of the swarms reported in the experiment.

Active particles and tissues on flat substrates (T2 and T3):
In collaboration with Dr. Giorgio Volpe (consultant), leading experiments at the University College London, we studied the propagation of chiral bacteria on substrates with micro-obstacles. We showed that instead of hindering propagation, an optimal, relatively low obstacle density significantly enhances the propagation on surfaces due to individual forward-scattering events. This finding provides insight on the emerging dynamics and inspires possible routes to control microbial ecology in natural habitats. With the group of Dr. Miguel Oliveira, at the 3Bs (Univ. Minho), we studied cell adhesion and proliferation on substrates. They performed experiments with tumoral cells (glioblastoma multiform), cultured in vitro and obtained data for the position of each cell over time. We developed an algorithm to post-process the experimental images and a numerical model to study the dynamics, showing that there are three relevant mechanisms: motility, cell-cell interaction, and cell division. We found a

significant reduction of the cell interaction as a response to the local increase in cell density, which is consistent with a known biological mechanism of contact inhibition and motility enhancement for cancer cells.
The structure and dynamics of tissue cultures depend strongly on the properties of the underlying substrate. The use of patterned culture surfaces has been proposed as an effective way to induce space-dependent properties in cell tissues. However, cells move and diffuse, and the transduction of external stimuli to biological signals is not instantaneous. We developed a numerical model based on the self-propelled Voronoi model where we consider the adaptation time and showed that it sets a minimum length scale for the fidelity of the pattern. We also studied the effect of spatial heterogeneities of the substrate. We showed that the larger the strength of the heterogeneity, the lower the tissue rigidity, a relevant finding for the control of cell motility of tissues in vitro through the substrate properties.

Cells in 3D scaffolds (T4):
With Prof. João Mano, leading experiments at CICECO at the University of Aveiro, we studied cells in 3D scaffolds. Combining kinetic Monte Carlo simulations of a lattice model, Langevin dynamics, and mean-field Smoluchowski equations, we studied the spontaneous formation of cell-mediated colloidal scaffolds. We showed that the size of the scaffolds is optimized if cell-cell adhesion is suppressed in the initial stage of aggregation, with an optimal number of cells per colloid, which depends on the ratio of the diffusion coefficients of colloids and cells. We have also studied the interactions of living adherent cells with a granular bed of spherical particles. Combining experimental results and in-silico model, we provided an explanation for the observed dependence of the survival probability on the size of the particles, and we proposed a time-dependent biological mechanism of cell adhesion.
To design distinct yet continuous living tissues it is necessary to obtain gradients of non-living and living entities. With Dr. Miguel Oliveira and Prof. Rui Reis, at the 3Bs (Univ. Minho), we have shown that these spatial patterns can be obtained in mixed hydrogels, by inducing thermal gradients in two injected fluid systems, preserved through the sol-gel transition. We developed a numerical model to validate the initial hypothesis and identify the regime of parameters for each targeted pattern.

Mechanical properties of cells and tissues (T5):
In the limit of low activity, we have shown that, although there is no rigidity transition in confluent tissues, there are profound changes in the structure of

the energy landscape. We found two disordered solid phases that have similar structural features but differ in the ultrametricity of their energy landscapes; the crossover between these two states shares features with the Gardner transition. In collaboration with Dr. António Jacinto (consultant) and Dr. Lara Carvalho, from Univ. Nova de Lisboa, we studied wound closing in epithelial tissues. We combined live imaging and theoretical modelling to propose that occluding junctions are essential for wound closure by impacting on epithelial mechanics at the tissue level, which in turn is crucial for correct regulation of the cellular events occurring at the wound edge. To study the mechanics of wound opening in a viscoelastic, isotropic, homogeneous, and incompressible thin tissue, we developed a continuous approach, based on Kelvin-Voigt's model. We found that the regimes of deformation are defined by a single dimensionless parameter, which characterizes the relative importance of viscosity over friction. We also developed a discrete model to study the impact on wound healing of heterogeneities in the spatial distribution of cell types. Several experimental results reveal a non-trivial dependence of the healing time on the heterogeneity of cells. Our model suggests that this might be driven by a heterogeneous distribution of the strength of friction with the substrate.

Resultados Atingidos

This work led to 30+ publications in Q1 journals, which include 3 Nature Communications, 2 ACS Applied Materials & Interfaces, 1 Applied Materials Today, 1 Journal of Cell Biology, 9 Soft Matter, and 1 Biophysical Journal. 2 PhD and 5 MSc theses have been completed, and 4 PhD awards are expected within the next year. This grant also provided the necessary conditions to consolidate the international network of collaborators and attract complementary funding, namely, 1 ITN Marie Curie, 3 CEEC Individual contracts from FCT, and 3 PhD fellowships from FCT.