# Emmy Noether Junior Research Group

The main interest of our group is the role which material properties play for the functioning of biological cells. In particular, we are interested in the role of forces and elasticity in cell adhesion. Other interests of our group relate to the theoretical understanding of biomaterials. For example, we investigate the structural properties of spatially extended structures in lipid-water mixtures.

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## Forces and Elasticity in Cell Adhesion

It is well known, especially in the medical community, that mechanical input is essential for proper functioning of certain cell types, including tissue cells from bone, lung and blood vessels (which under physiological conditions are subject to permanent strain through body movements, breathing and blood pulsation, respectively). During the last year, there has been a large effort to clarify the underlying mechanisms on the level of single cells. It is now clear that most adherent cells not only react to external force in a specific way, but also that cells actively exert force on their environment in order to probe its mechanical properties (active mechanosensing).

For cells adhering to extracellular matrix, the force transmitting sites of adhesions are the so-called focal adhesions. In collaboration with cell biologists at the Weizmann Institute in Israel, we were able to show that internally generated force and lateral size of focal adhesion correlate in a linear way, with a stress constant of 5.5 nN/$\mu m^2$ **[1]**. For this study, we developed a new technique to reconstruct forces at single focal adhesions from the deformations of a micro-patterned elastic substrate, namely by numerically solving the ill-posed inverse problem of linear elasticity theory **[2]**. **Fig. 1** shows the reconstructed forces exerted by a fibroblast at fluorescently labeled focal adhesions.

Since elastic deformations are long-ranged and sensitively depend on boundary conditions of the surrounding medium, cells might sense external perturbations, mechanical activity of other cells or geometrical features like boundaries through local mechanosensing. Using defect theory and linear elasticity theory, we developed several models for cell organization in soft media **[3, 4]**. Force patterns of polarized cells are typically pinch-like and can be modeled as anisotropic force contraction dipoles. The surrounding medium is assumed to behave like an isotropic elastic medium, which applies to many synthetic elastic substrates and which is expected to be a good approximation for hydrogels on large time and length scales. For the cellular reaction to strain, in one model we assumed that the cells react like inert physical particles **[3]**. This case might apply to artificial cells with a contractile system but without biochemical regulation. We found that cellular structure formation is similar to the case of electric quadrupoles, with neighboring cells orienting perpendicular to each other. In order to model the behavior of cells with regulated response, we started from the observation that growth of focal adhesions might be triggered by a threshold in force. Since build-up of force is more efficient in a stiff environment, we suggested that cell processes are favored which proceed in a direction of large effective stiffness **[4]**. We found that in this case, cells line up in strings, exactly as observed experimentally. In regard to boundary effects, we were able to show that cells align perpendicular and parallel to clamped and free boundaries, respectively, again in excellent agreement with experimental observations **(Fig. 2)**.

## Cubic Phases in Lipid-Water Mixtures

Different ordered phases are known to form in lipid-water mixtures, including lamellar, hexagonal and cubic bicontinuous phases. The cubic phases have been found to form in many membrane-rich regions of cells and are used for crystallization of membrane proteins. In a bicontinuous structure, one highly convoluted interface spans the whole sample, thereby dividing it into two separate labyrinths **[5]**. Since surfaces with vanishing mean curvature (minimal surfaces) minimize the bending energy of lipid bilayers, triply periodic minimal surfaces are the main structural models for ordered bicontinuous phases in lipid-water mixtures. Here the mid-surface of the lipid bilayers corresponds to the minimal surface, while the neutral surfaces of the two lipid monolayers correspond to parallel surfaces to the minimal surface **(Fig. 3)**.

Although there are a large number of different cubic minimal surfaces, in lipid-water mixtures only the structures G, D, P and I-WP have been identified experimentally **[5]**. In our theoretical work, we showed that phase behavior is determined by the distribution of Gaussian curvature over the minimal mid-surface. In detail, we found that the relative stability of the different cubic phases is determined by the dimensionless quantity $\Delta$, which characterizes the width of this distribution **[6, 7]**. G, D and P have the same small value of $\Delta$ because they belong to the same Bonnet family. I-WP has a larger value and thus needs stabilization through additional physical mechanisms to become stable. All other structures have even larger values, which explain why they are not observed in experiments. Moreover, we found that the sequence of phases with increasing water content is determined by the dimensionless topology index, which describes the porosity of the structure. This explains the generic sequence G – D – P found in experiments when increasing water content.

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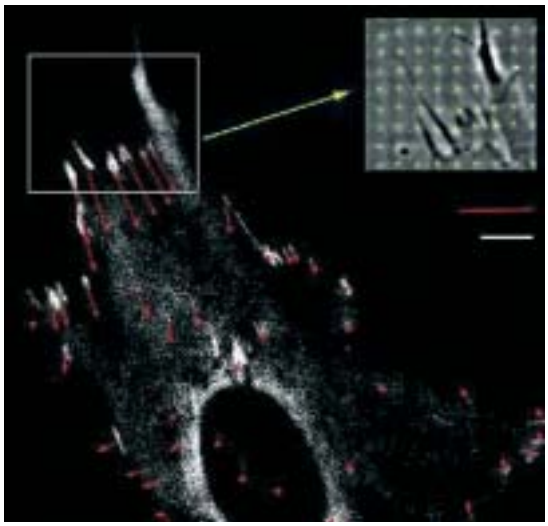

*Fig. 1: Forces (red) exerted by an adhering fibroblast at sites of focal adhesions (white) which are fluorescently labeled. The inset shows a phase contrast image of the deformation of the micro-patterned elastic substrate (green), from which the force pattern has been calculated. White bar = 4 µm, red bar = 30 nN.*

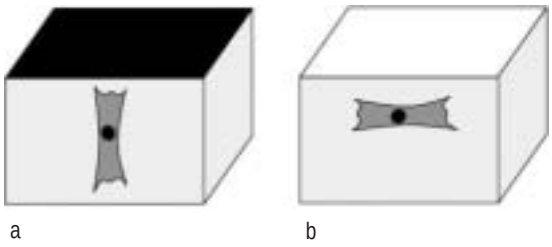


*Fig. 2: Mechanically active cells in soft media align (a) perpendicular to clamped boundaries and (b) parallel to free boundaries, because in this way, they sense an effective increase in stiffness, which is favorable for growth of focal adhesions.*

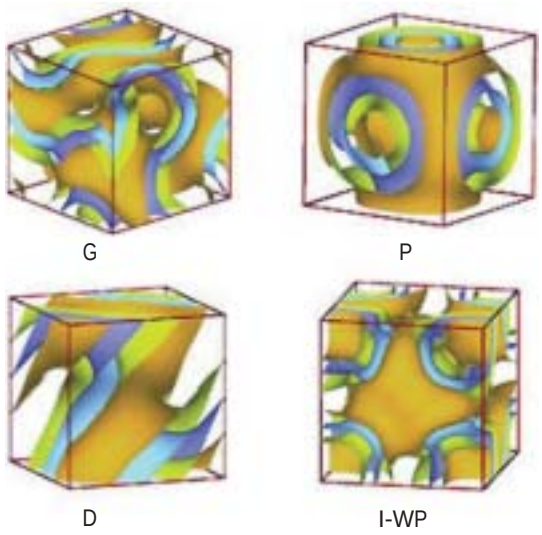


*Fig. 3: Models for cubic bicontinuous phases in lipid-water mixtures: the mid-surface of the lipid bilayer is a triply periodic minimal surface (blue). The two parallel surfaces are the neutral surfaces of the lipid monolayers (orange).*

**References:**

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