Probing cell mechanics with photoacoustic and photothermal methods

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Background – Biological cells are soft and micron-sized objects. The past decade has shown an acceleration in technological possibilities to characterize their mechanics [1], thanks to advances in nanotechnology and quantitative micromanipulation. Existing techniques, among which atomic force microscopy (AFM), micropipette aspiration, and magnetic twisting cytometry, require contact/invasive interrogation [2] with the cells, which can not only cause unintended cell damage but also lead to significant over/under-estimation of the measured values because of the complicated linkages between probes (size, shape, stiffness) and cells. Furthermore, these techniques are often limited to the surface of the cells and they hardly provide information about the internal cell structure, e.g., the cytoskeleton and the nucleus. Therefore, non-contact, non-invasive, and non-destructive techniques for assessing cell mechanics need to be developed in the field of cell mechanics and cell mechanobiology.

Methods – Combining light, heat, and sound, photoacoustic (PA) and photothermal (PT) approaches [3] have reached a mature state for non-contact and non-destructive thermal, mechanical, and interfacial bonding characterization of a variety of materials and layered structures in solid-state physics. This work aims at exploring PA and PT measurement approaches on a microscale on biological cells, thereby addressing the above-mentioned challenges in experimental cell mechanics, including the assessment of contact mechanics at the cell-substrate [4] (e.g., cell adhesion) and intracellular mechanics [5] (e.g., viscoelasticity and compressibility). The quality of contact between a cell and its surroundings can be probed directly by applying and measuring forces and displacements statically or by looking at the transmission and reflection of acoustic waves. An alternative way is by looking at thermal diffusion through the interface by a contactless photothermal approach.

Results – In this work, we demonstrate the application of the photothermal transient thermo-reflectance technique to probe the quality of the contact at the cell/substrate adhesion interface. We study nanoscale thermal transfer across the interface, thus assessing the boundary thermal resistance related to the presence of the adhesion sites. Fig. 1 illustrates the concept and workflow of PT imaging of cell-substrate adhesion with the developed TTR microscope (**A**), in which a pulsed laser (blue) is used to launch transient thermal waves, and their diffusion across the cell adhesion interface is monitored by a continuous wave (CW) probe laser (green). The built-in bright-field microscope and the scanning stage allow to allocate the pump-probe beams onto the interface beneath the cell under study (B). The TTR signals are different at different locations (C). By performing a 2D raster scan, we can image an entire cell with 1-micron lateral resolution (D). Theoretical simulation by a 1D three-layer thermal diffusion model suggests the TTR signals are sensitive to the interfacial thermal resistance, R_{th}. Our results illustrate that the photothermal TTR technique is a feasible tool for non-contact, non-invasive, and quantitative assessment of cell-substrate adhesion with sub-micron resolution.

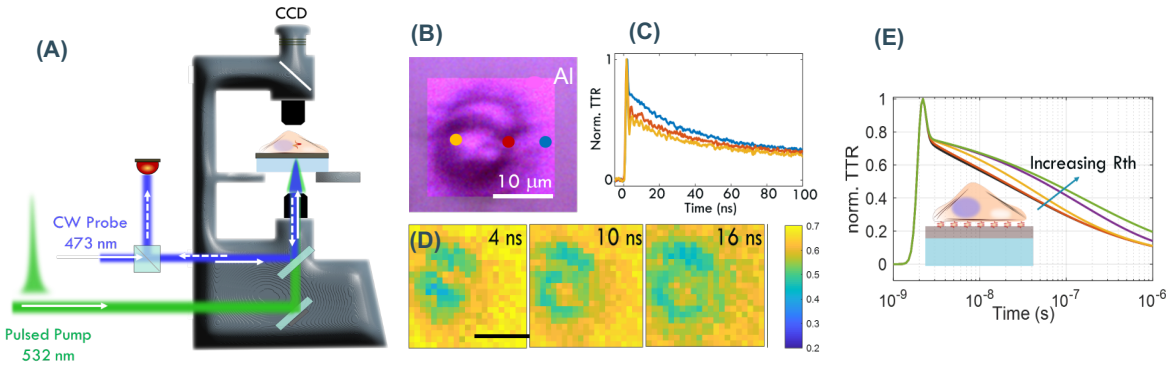

Fig. 1. Schematic illustration of the PT imaging of a single cell on a substrate: (**A**) experimental setup, (**B**) an optical bright-field image of a neuron cell under study, (**C**) Three representative TTR waveforms recorded at the three positions indicated in (B). (**D**) Three snapshots of the thermal wave images with ns time-resolution. On such short time scales, thermal waves ***penetrate cells <100 nm***, estimated by $(\alpha t)^{1/2}$ with α the thermal diffusivity, about 10^{-7} m^2/s for cells. (**E**) the effect of R_{th} on TTR signals simulated by using a 1D three-layer thermal diffusion model. R_{th} values are 10^{-8}, 10^{-7} , 10^{-6} , 10^{-5} Km^2/W, from bottom to top, respectively.

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