Tissue Dynamics Spectroscopy of Multicellular Tumor Spheroids

Biodynamic imaging uses fluctuations in backscattered light intensities to connect to the intracellular motions inside living tissue. The fluctuations have characteristic frequencies depending on the speed of the intracellular constituents, much like the Doppler effect. By calculating the fluctuation power spectrum, one gets information at all the different time scales and hence at all the different speeds. This is called fluctuation spectroscopy, and when performed with biodynamic imaging it is called tissue dynamics spectroscopy (TDS).

Tissue dynamics spectroscopy typically extends over three orders of magnitude in frequency, from 5 Hz to 0.005 Hz. This frequency range captures organelle transport like mitochondria and endosomes, nuclei motions, intra-nuclear motions of the nucleoli, membrane undulations and finally, at the lowest frequencies, cellular rheology as cells respond to their force environment.

**Fig. 1** Examples of drug-response spectrograms for Iodoacetate and Cytochalasin D. Time is along the horizontal axis, and the fluctuation spectral analysis is along the vertical axis. These spectrograms are differential relative values that track the changes in the spectral power relative to the original power spectrum. Both spectrograms rat osteogenic sarcomas. Iodoacetate is a metabolic drug that influences glycolysis, while Cytochalasin D is a anti-actin drug. Glycolysis is a known biochemical oscillator, and the spectrogram shows a low-frequency oscillation with a 40 minute period. Cytochalasin D causes the actin cortex to degrade, decreasing the stiffness of the membrane and causing enhanced membrane undulations. After 4 hours, the onset of a new frequency pattern is consistent with apoptosis.
Tissue dynamics spectroscopy uses the frequency of backscattered light fluctuations to “tag” the dynamical mechanisms inside the cells in the living tissue. High frequencies correspond to objects that move quickly, such as mitochondria and endosomes. Low frequencies correspond to the lowest speeds, such as the slow relaxation of cells and tissue to forces in a rheological response.

These motional “tags” are obtained from as deep as 1 mm inside the tissue, in a non-fluorescent and noninvasive approach that enables continuous time monitoring after the application of a pharmaceutical. Tissue dynamics spectroscopy has rich information content, with high specificity to discriminate among subtle differences in cell lines and drug responses. All the drug responses are from three-dimensional con-texts and hence more faithfully capture the natural drug response.

References:

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