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Imaging and Analysis Applications for Decoding Complex Biological Signalling Profiles

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Extended Abstract

As biomedical research advances toward resolution of complex biological signals and systems, new approaches and tools are needed to decipher critical processes and define features of homeostasis and disease. Our lab and others have focused on quantifying spatially and temporally distinct signalling patterns within continuous cell networks of intact biological tissues. [1] Using high-speed, high-resolution imaging approaches coupled with novel custom analysis algorithms, we have begun to decode the spatial and temporal tuning of key intracellular signals that underlie the degree and specificity of biological responses.

In the current study, our objective was to apply our dynamic image analysis package along with a targeted (fluorescent) biosensor-expressing mouse model (cdh5-GCaMP8) [2] to determine the functional Ca^{2+} signalling profile of the vascular endothelial cell networks within isolated blood vessels and the lung microcirculation. Free Ca^{2+} is one of the most fundamental and ubiquitous second messenger signals in all of biology and disrupted Ca^{2+} signalling is inherently linked to multiple disease states. [3] Unlike previous static region-of-interest analysis that often fails to adequately capture signals (e.g., signals from fluorescent intracellular Ca^{2+} indicators) through space and time, tracking dynamic regions of interest allows for complete quantification of holo-signal events by adapting to the footprint of the signal over its lifetime [4], even within complex multi-cellular networks. Integration of cutting-edge image processing and particle tracking approaches has allowed us to evaluate and characterize multiple complex cellular systems and discern intrinsic signalling patterns based on profiles of signal parameters including frequency, amplitude, duration, spatial spread and time-extrapolated volume.

Here, we conducted live-tissue confocal imaging experiments using opened artery and organ slice preparations from cdh5-GCaMP8 mice to determine the distinct signalling signatures of complex endothelial networks. Targeted expression of the GFP-based Ca^{2+} indicator only within the endothelium (monolayer of cells lining the internal surface of the entire vasculature) allowed for isolation and detection of rapid endothelial cell signal transients along the vascular wall using spinning disk confocal imaging. Through application of our novel dynamic region of interest tracking and multi-parameter mapping, we revealed inherent signalling signatures along the cellular network that represent predictable profiles of network homeostasis not previously been characterized. We also demonstrated and characterized the distinct tuning of these signature parameters by physical perturbations, including changes in sheer stress, temperature, and pH. In particular, discrete adjustment of signal frequency and spatial spread appear to be key features of signal control and specificity. In future investigations, current approaches will be extended into applications for pattern recognition, including the definitive identification of homeostatic-to-pathologic pattern switching associated with diseases such as atherosclerosis. [5]

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