High-Throughput, High-Fidelity Reconstruction Of Whole Mouse-Heart Cytoarchitecture At Cellular Scale

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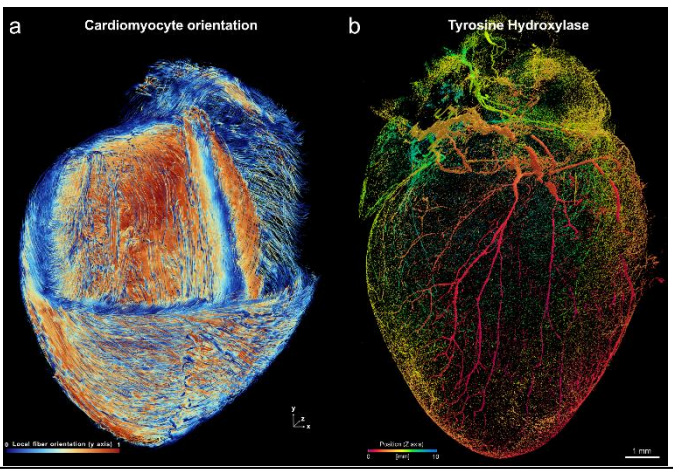
Three-dimensional reconstruction of myocardial fibre and sheet architecture is essential for biophysical cardiac models, yet acquiring these data at the whole-organ scale with sufficient resolution remains challenging. We present a high-throughput imaging pipeline that combines CUBIC tissue clearing optimized for cardiac tissue, dual-camera light-sheet microscopy, and an automated dual-view fusion algorithm. Whole mouse hearts (n = 9) are imaged label-free, exploiting intrinsic myocardial autofluorescence at 3.25 × 3.25 × 3 μm³ voxel size in ~25 minutes per sample. Dual-view fusion effectively eliminates depth-dependent signal degradation, yielding isotropic-quality image stacks suitable for automated structural analysis. From these data, we extract transmural profiles of helix angle and sheet angle across the entire ventricular walls with an isotropic resolution of 100 μm³, recovering the well-established progressive rotation of cardiomyocyte orientation and the regional heterogeneity of laminar organization. These morphometric outputs are directly usable as fibre-field inputs for eikonal and reaction–diffusion models of cardiac electrophysiology. The pipeline is compatible with fluorescent reporters and whole-mount immunostaining, demonstrated here by reconstructing the cardiac sympathetic innervation throughout the intact organ. By providing rapid, scalable, and model-ready cytoarchitectural data, this approach bridges mesoscale imaging and computational cardiology in physiological and pathological models.



a) 3D reconstruction of locally prevailing cardiomyocyte orientations orientation throughout whole mouse heart ventricles, rendered as streamlines. b) 3D reconstruction of sympathetic nervous system in a CUBIC-cleared adult mouse heart, acquired by mesoSPIM².