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## Deep-SegCLEM: unified segmentation and matching for correlative light–electron microscopy

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Correlative light and electron microscopy (CLEM) links dynamic functional imaging with ultrastructural detail, yet automated correlation remains unresolved due to the difficulty of bridging two fundamentally different microscopy modalities. Current approaches either bypass segmentation or rely on generic models, leading to poor or inconsistent alignment. We present Deep-SegCLEM, a fully automated pipeline that leverages mitochondria-specific features to establish fiducial-free correspondence between LM and EM images. Deep-SegCLEM integrates two tailored segmentation networks—DSCLEM-LM for fluorescence microscopy and DSCLEM-EM for electron microscopy—with a multi-scale template-matching algorithm for cross-modal alignment. On fluorescence datasets spanning confocal, Airyscan, and SIM modalities, DSCLEM-LM achieved state-of-the-art performance ( $F1 = 0.98$ ,  $IoU = 0.96$ ), surpassing U-Net, U-Net++, DeepLabV3, FCNN, MitoSegNet ( $F1 = 0.93$ ), and the  $\mu$ SAM foundation model ( $F1 = 0.73$ ). DSCLEM-EM similarly outperformed classical CNN architectures and foundation models across multiple public EM benchmarks, including challenging conditions such as UroCell ( $F1 = 0.80$  versus  $\leq 0.57$  for CNN baselines and  $\leq 0.72$  for  $\mu$ SAM). Failure-Driven Targeted Augmentation (FDTA) was essential for capturing rare morphologies and improving generalization. The correlation module achieves fully unsupervised LM–EM alignment in minutes, with over 80% matching accuracy and a mean centroid error of  $2.0 \mu\text{m}$  relative to expert-generated STED–EM correspondence. Additional fluorescence channels are automatically co-registered with EM ultrastructure, enabling mechanistically meaningful mapping of molecular events. Using HALO-BAK and Drp1, Deep-SegCLEM associates apoptotic membrane discontinuities and mitochondrial fission sites with their ultrastructural counterparts, demonstrating biological relevance. Together, these advances deliver a scalable, end-to-end workflow for quantitative, fiducial-free correlative microscopy, enabling high-throughput mapping of molecular signals to ultrastructure during dynamic cellular processes.

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