High-throughput zebrafish 3D imaging system for heterogeneous studies

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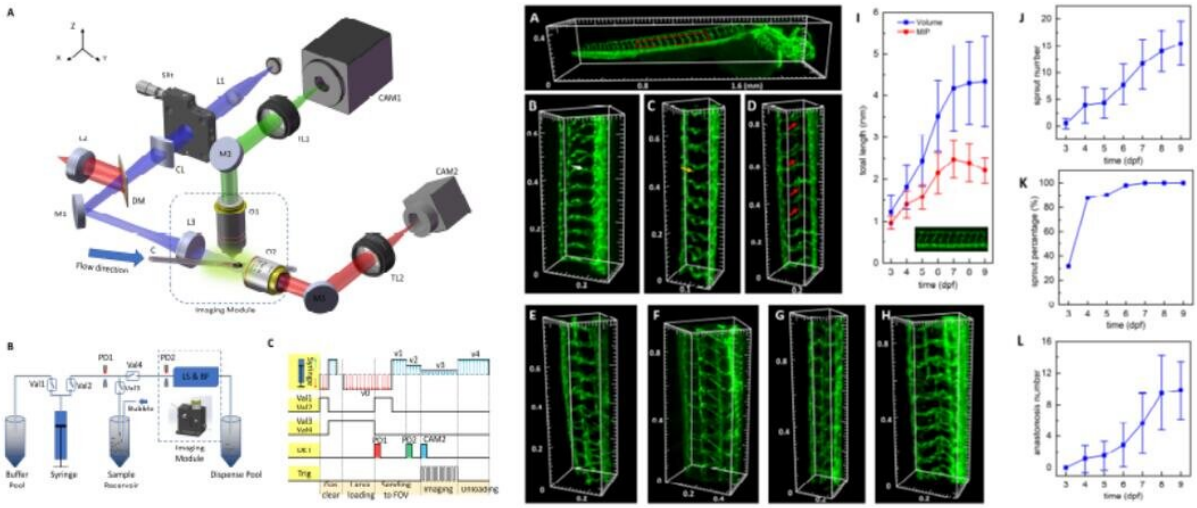

Schematic diagram of the high-throughput 3D imaging system LS-FIS (left) and statistical study of the vascular development process from 3 to 9 dpf for hundreds of zebrafishes (right). Credit: SIBET

Zebrafish have been widely used in developmental biology, immunology, neurobiology, and drug screening, showing significant superiority in large-scale heterogeneous studies of development and drug effects due to their small size, short life cycle, high fecundity, and low cost. However, practical experiment processes rely heavily on hand manipulation and imaging under traditional microscopes with large workloads but very low efficiency, which limits the use of zebrafish in large-scale analysis.

To address these bottlenecks, researchers at the Suzhou Institute of Biomedical Engineering and Technology (SIBET) and Shanghai Institute of Nutrition and Health (SINH) of the Chinese Academy of Sciences (CAS) have developed a light-sheet flow imaging system (LS-FIS) for high-throughput three-dimensional (3D) imaging of zebrafish.

Light-sheet microscopy is a 3D imaging method with low phototoxicity and fast imaging speed. However, current light sheet imaging requires a complex sample preparation process for zebrafish imaging. Moreover, due to the limited field-of-view, 3D imaging of whole embryos often requires multi-region imaging and stitching, which severely limits the imaging flux of this technique.

Through a smart design of fluid flow and optical coupling system with precise sampling control timing and 3D reconstruction algorithms, the researchers combined flow imaging technology with light sheet illumination to achieve high throughput 3D imaging of 200 embryos/hour.

LS-FIS was applied to study the development of blood vessels in the trunk and head of zebrafish. 100 transgenic zebrafish Tg(kdrl: EGFP), whose vascular endothelial cells labeled with green fluorescent protein were imaged daily with LS-FIS from three to nine days post-fertilization for demonstration.

More than 500 3D images of whole embryonic zebrafish were obtained, which is the first known report of large-scale whole-fish 3D imaging data.

Prototype of the high-throughput 3D imaging system LS-FIS exhibited at the China Zebrafish Conference 2021. Credit: SIBET

The researchers measured and analyzed the length of intersegmental vessels and changes in the morphology of the hyaloid vascular with the obtained 3D structures. Results show significant heterogeneity of the trunk vessel development but less heterogeneity of the hyaloid vascular.

This work, titled "Heterogeneities of zebrafish vasculature development studied by a high throughput light-sheet flow imaging system," was published in *Biomedical Optics Express*.

In addition, the prototype of LS-FIS has been validated for several iterations for better stability, appearance, and easy-to-use software interface. It was also tested in the SINH and the Institute of Neuroscience of CAS and proved to have a good imaging capability and

versatile usage.

The researchers further developed relevant image analysis and processing algorithms to deal with large amounts of 3D image data captured by LS-FIS. For zebrafish intersegmental blood vessels, they proposed a 3D convolutional neural network with multiscale features (MS-3D U-Net) to achieve segmentation and recognition of 3D vascular. By multiscale feature learning and an optimized loss function based on a hard attention mechanism, MS-3D U-net achieved an accuracy of over 90% (AUC value).

Based on MS-3D U-Net, they automatically segmented and measured the 3D image data of zebrafish embryos that were continuously observed for 24 hours and plotted the developmental curves of intersegmental vessels and dorsal longitudinal anastomosing vessels.

Relevant results, titled "Optimized U-Net model for 3D light-sheet image segmentation of zebrafish trunk vessels," were also published in *Biomedical Optics Express*.

More information: Guang Yang et al, Heterogeneities of zebrafish vasculature development studied by a high throughput light-sheet flow imaging system, *Biomedical Optics Express* (2022). DOI: 10.1364/BOE.470058

Jingyi Yin et al, Optimized U-Net model for 3D light-sheet image segmentation of zebrafish trunk vessels, *Biomedical Optics Express* (2022). DOI: 10.1364/BOE.449714

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