SYSTEM-LEVEL RECONSTRUCTION OF DEVELOPMENT WITH LIGHT-SHEET MICROSCOPY

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In embryonic development of vertebrates and higher invertebrates, a single cell is transformed into a fully functional organism comprising tens of thousands of cells. In a complex process of self-organization, these cells rapidly divide, migrate, differentiate and form tissues and organs able to perform the most challenging tasks. The nervous system is a key component of the developmental building plan that stands out in terms of size, complexity and function. However, very little is known about the developmental dynamics of this complex system, since the technology to comprehensively record and computationally analyze in vivo cell behavior in neural tissues is lacking. The overall objective of our research is to gain such quantitative experimental access, to determine the fundamental rules governing neural development, and to systematically link development to the functional activation of circuits in the nervous system.

I will present our experimental approach based on light-sheet fluorescence microscopy, an emerging imaging technology that achieves exceptionally high imaging speed and signal-to-noise ratio, while minimizing light exposure of the specimen. This unique combination of capabilities makes light-sheet microscopes indispensable for the long-term in vivo imaging of entire developing organisms. We are designing advanced implementations of scanned light-sheet fluorescence microscopy, such as the SiMView technology framework for simultaneous multiview imaging [1], to systematically study the early development of entire fruit fly, zebrafish and mouse embryos with cellular resolution. I will furthermore present strategies for automated large-scale image processing, advanced specimen culturing techniques and new transgenic reporter lines. Together, these tools allow us to perform whole-organism functional imaging and quantitatively analyze developmental lineages and their interrelationships in the entire animal [2]. Our goal is to take advantage of these high-resolution data to attain a system-level understanding of cell fate decisions and how they establish the dynamic architecture of neural tissues. In the long-term perspective, we will use this information for the establishment and validation of a computer model of the developing nervous system.

I envision that our quantitative approach to the reconstruction of large neuronal system dynamics will provide critical insights into the properties of complex circuits and complement ongoing large-scale electron microscopy analyses of static neuronal network architecture.