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Light Sheet Fluorescence Expansion Microscopy: Fast Mapping of Neuronal Connectivity at Super Resolution

Understanding the architecture of neural circuits is an important but formidable task. Critical details of neuronal connectivity - the synapses - occur on length scales of about 100 nm. Thus, imaging techniques reaching optical super resolution are required. However, neurites extend over distances of millimeters and centimeters, thus optical sectioning, a large field of view and a high imaging speed is required to cope with these complex 3D structures in an acceptable amount of time. Here we combined tissue expansion and light sheet fluorescence microscopy to allow volumetric of large mouse brain samples. These two methods are an ideal match to obtain super-resolved images of extended neuronal circuits with three distinctive features, namely high imaging rates of up to 40 Hz, high contrast and low photobleaching. We demonstrate the capabilities of our method by comparing it with high resolution confocal laser scanning microscopy using an Airyscan detector to obtain detailed high-resolution images of extended neuronal networks from the hippocampal mouse dentate gyrus (DG). The Airyscan approach delivers high-resolution images featuring a lateral and axial resolution of 120 and 400 nm, respectively, for green fluorescence, but with limited contrast and a prohibitively low frame rate of 0.1 Hz, considering the necessity to image the complete DG region of ~1mm^3. Using light sheet fluorescence expansion microscopy we achieved a virtual lateral and axial optical resolution of 75 and 450 nm, respectively, thus performing fast volumetric super resolution imaging of mouse dentate gyrus. Our approach allows us to observe autofluorescent proteins, thus avoiding antibody staining. In combination with Rabies virus staining, specific cell types and selected connections between neurons may be studied. In this manner neural connections can be mapped throughout axially extended brain sections allowing a better segmentation of DG granule cell neurites for further morphology analysis.

Affiliation

Institute of Physical and Theoretical Chemistry, University of Bonn

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Primary author(s) : Mr RODRIGUEZ, Juan Eduardo (Institute of Physical and Theoretical Chemistry, Rheinische Friedrich-Wilhelms-University Bonn, Wegelerstr. 12, 53115 Bonn, Germany)

Co-author(s) : Ms PAVLOVA, Irina (Functional Neuroconnectomics Group, Institute Experimental Epileptology and Cognition Research, Rheinische Friedrich-Wilhelms-University Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany); Mr HERBST, Marius (Institute of Physical and Theoretical Chemistry, Rheinische Friedrich-Wilhelms-University Bonn, Wegelerstr. 12, 53115 Bonn, Germany); Ms BÜRGERS, Jana (Institute of Physical and Theoretical Chemistry, Rheinische Friedrich-Wilhelms-University Bonn, Wegelerstr. 12, 53115 Bonn, Germany); Mr RULAND, Jan (Institute of Physical and Theoretical Chemistry, Rheinische Friedrich-Wilhelms-University Bonn, Wegelerstr. 12, 53115 Bonn, Germany); Dr SIEBRASSE, Jan Peter (Institute of Physical and Theoretical Chemistry, Rheinische Friedrich-Wilhelms-University Bonn, Wegelerstr. 12, 53115 Bonn, Germany); Dr SCHWARZ, Martin K. (Functional Neuroconnectomics Group, Institute Experimental Epileptology and Cognition Research, Rheinische Friedrich-Wilhelms-University Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany); Prof. KUBITSCHECK, Ulrich (Institute of Physical and Theoretical Chemistry, Rheinische Friedrich-Wilhelms-University Bonn, Wegelerstr. 12, 53115 Bonn, Germany)

Presenter(s) : Mr RODRIGUEZ, Juan Eduardo (Institute of Physical and Theoretical Chemistry, Rheinische Friedrich-Wilhelms-University Bonn, Wegelerstr. 12, 53115 Bonn, Germany)

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