MAR13-2012-020341

Abstract for an Invited Paper
for the MAR13 Meeting of
the American Physical Society

Voltage imaging in vivo with a new class of rhodopsin-based indicators

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Reliable, optical detection of single action potentials in an intact brain is one of the longest-standing challenges in neuroscience. We have recently shown that a number of microbial rhodopsins exhibit intrinsic fluorescence that is sensitive to transmembrane potential. One class of indicator, derived from Archaerhodopsin-3 (Arch), responds to voltage transients with a speed and sensitivity that enable near-perfect identification of single action potentials in cultured neurons [Nat Methods. (2011). 9:90-5]. We have extended the use of these indicators to an in vivo context through the application of advanced imaging techniques to the larval zebrafish. Using planar-illumination, spinning-disk confocal, and epifluorescence imaging modalities, we have successfully recorded electrical activity in a variety of fish structures, including the brain and heart, in a completely noninvasive manner. Transgenic lines expressing Arch variants in defined cells enable comprehensive measurements to be made from specific target populations. In parallel, we have also extended the capabilities of our indicators by improving their multiphoton excitability and overall brightness. Microbial rhodopsin-based voltage indicators now enable optical interrogation of complex neural circuits, and electrophysiology in systems for which electrode-based techniques are challenging.