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Synthetic development of voltage sensitive dyes for two-photon voltage imaging

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The detailed understanding of neuron activity and network structures holds the promise of new treatments for neurological diseases and the development of the next generation of brain–computer interfaces. To effectively study neurons, the spikes of swift membrane potential change should be detectable and observable over time. Genetically encoded voltage indicators (GEVIs), such as ASAP5 or JEDI-2P, are emerging tools to capture changes directly in neuronal membrane potential with fluorescence microscopy. Certain experimental systems, such as those involving ex vivo human tissue, are not compatible with the expression times of virally delivered GEVIs, that may be as long as several weeks. Voltage sensitive dyes (VSDs) enable ready voltage imaging through the fast staining of cell membranes, but the currently available sensors are limited by their low fluorescence enhancement and brightness. Available VSDs that perform well in two-photon microscopy are especially limited. A better understanding of the voltage sensing mechanism and a facile screening method of candidate molecules could lead to the development of more efficient VSDs. This work is focused on several aspects of VSD development. First, the role of the lipophilic wire part of a prominent VSD (RhoVR) will be systematically modified synthetically and studied by computational methods to explore its role in the voltage sensing mechanism and to identify a pathway to property improvements. Second, novel VSDs are synthesized based on a tetraoxaazapentacene fluorophore to achieve high photostability and improved two-photon fluorescence properties. Finally, the novel VSDs are tested in single-photon spectroscopic experiments using a liposomal system and two-photon microscopic experiments with HEK cells.