

PROJECT SUMMARY (See instructions):

Neurotransmitters regulate synaptic transmission in the nervous system. A technique that allows targeted delivery of neurotransmitters with high spatiotemporal precision would facilitate the study of neurotransmitter function in neural networks. Current techniques such as so-called “caged compounds” offer both spatial and temporal control of transmitter release upon light activation. However, despite these advantages caged compounds suffer from (1) the limited number of compounds that are available for neuroscience, and (2) relatively low release efficiency with near-infrared (NIR) light that has the advantages of lower photo-toxicity and high tissue penetration. In this project, we will develop a versatile liposome encapsulation and burst release system that can provide localized and temporally well-defined delivery of neuroactive molecules; and use this system to modulate neuronal functions. Specifically, liposome is an artificially-prepared spherical vesicle composed of a lamellar phase lipid bilayer and will encapsulate the neurotransmitter glutamate along with plasmonic gold nanorods. Upon pulsed NIR light excitation, the gold nanorods locally heat up within a few nanoseconds to create nanoscale cavitation bubbles (i.e. nanobubble) and disrupt the liposome membrane to burst release the neurotransmitter. In this project, we will first characterize the burst release response as a function of laser intensity, liposome size, and encapsulated gold nanorod concentration, and simultaneously image the release and millisecond diffusion kinetics immediately after pulse laser irradiation. We will then apply the novel neurotransmitter release technique to modulate neuronal activity in cell cultures and brain slices. Following the focused beam irradiation and burst release of glutamate, we will characterize synaptic responses and changes in cell excitability (i.e. action potential firing) with electrophysiology. If successful, the liposome burst release technique will be a valuable new tool for neuronal modulations through biochemical interaction, which will benefit basic neurophysiology and neurobiological research and potentially for studying neurological diseases and brain disorders. In particular, this technique will offer: (1) a versatile encapsulation and release method using liposomes to allow studying the effect of a broad range of neurotransmitters and other neuroactive molecules that cannot currently be used as “caged” compounds; (2) potential studies of interaction between multiple molecules in neuronal circuitry through multiplexing, i.e. by releasing different types of compounds with different NIR wavelengths; (3) a new technology that can be disseminated to neuroscience laboratories by incorporating micro-lasers.

RELEVANCE (See instructions):

The application aligns well with the intent of UT BRAIN seed grant program to foster new collaborations between diverse disciplines, which in this case are neuroscience (Kroener) and mechanical engineering (Qin). This proposed project develops a novel technology, i.e., payload burst release with spatial and temporal control and targeted delivery to understand basic neuroscience problems. This proposed project addresses Goal #4 (*Demonstrating causality: Link brain activity with precise interventional tools that change neural circuit dynamics*) and Theme #5 (*Validate and disseminate technology*) of the BRAIN initiative (BRAIN 2025 A Scientific Vision). The particularly novel aspect of this project is the highly localized and rapid (millisecond scale) release of a defined amount of neurotransmitter. The payload is extremely versatile since a large range of compounds can be encapsulated in the liposome from small molecules to large proteins, hydrophilic or hydrophobic. This unique tool, and in particular the burst release, has been developed only recently in the context of anti-cancer drug release and has not been used so far to answer challenging neuroscience questions. To carry out the proposed project, Dr. Qin will lead the development and implementation of the novel liposome burst release technique and Dr. Kroener will lead the design and implementation of electrophysiology and neurophysiology experiments. With the developed tools and the expected results from this UT Brain Initiative project the PIs will be well-positioned to compete for federal funding from NIH and NSF.