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LEDs and Lasers Battle for Dominance in Brain Research

Small but generally less powerful, or plenty of power but costly; the fight between LEDs and lasers in optogenetics intensifies.

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Lighting up the brain to better understand, treat or even cure brain disorders has become an established field known as optogenetics. First introduced in 2005 by professor Karl Deisseroth as he worked in a small laboratory at Stanford University, it has since been named Method of the Year by the journal Nature and is today one of the most promising tools making contributions to the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative — part of a new federal focus aimed at producing a dynamic picture of the brain.

Optogenetics research spreads

Today, optogenetics is flourishing in research laboratories all over the world and has made inroads in sleep and memory studies as well as with brain disorders such as Alzheimer's, depression and epilepsy. But there is debate over which light source is best suited for the job. While there's no doubt that both lasers and LEDs have advanced over the years in terms of power, efficiency and available wavelengths, further improvements in both sources could precipitate ground-breaking discoveries.

Lasers vs. LEDs: At a Glance

	Lasers	LEDs
Characteristics	High Intensity	Certain wavelengths are not powerful enough for in vivo experiments.
	Cannot be used wirelessly.	Ability to use wirelessly for light delivery.
Applications	High costs	Relatively low cost
	More complex configurations required compared with a single box LED module; care needs to be taken that the laser is being driven correctly — especially DPSSLs.	Fast rising rate and falling rate of light intensity, so can easily generate photopulses.
	For in vivo experiments in which light must be delivered into deep brain structures and affect a large volume of the brain, a laser is preferred for certain wavelengths for which there are no powerful LEDs.	Low power is not an issue for slice physiology (e.g., circuit mapping studies in brain slices) that do not require a deep penetration of the light into a large brain volume.
	Not appropriate for chronic modulation of brain function in the case of chronic brain disorders.	Small enough to be either carried by the animal research subject or implanted directly into the tissue of interest.
Future Potential	Development of ultraminiaturized laser modules could allow for headmounted experiments on awake, behaving animals.	Development of higher-intensity and wireless LEDs will significantly help the neuroscience field, contributing to a more thorough deconstruction of the neural circuits that contribute to social behavior as well as treating chronic brain disorders.

From an unassuming start at Stanford University, the father of optogenetics, Deisseroth, has since become an award-winning and much sought-after psychiatrist and neuroscientist with a large team behind him. One such researcher working closely with him is Jeanne Paz, professor at the Gladstone Institutes and the University of California, San Francisco, who believes the various devices that enable light to be delivered into the brain have been revolutionary in neuroscience.

“Optogenetic approaches allow us to express light-sensitive proteins on a membrane of a specific cell and to modulate its activity in real time with light — laser or LED,” Paz said. “This approach allows us to enhance or reduce the activity of specific cells and circuits as well as to switch their firing mode without altering their overall firing rate. These approaches allow us to interrogate the role of specific cells in the brain.”

Epilepsy research

One of the major applications has been to pinpoint which cells are causally involved in the pathological brain state that occurs during an epileptic seizure. Deisseroth, Paz and colleagues published a paper in *Nature Neuroscience* in 2013 outlining the approach they used to disrupt spontaneous epileptic seizures before they occur by targeting one specific cell type in the brain.

The team used a yellow diode-pumped solid-state laser (DPSSL) from Cobolt AB because the experiment required a high-intensity light source in order to target a large volume of the thalamus. It found that around 8 to 10 mW was sufficient to stop seizures. This would be impossible with yellow LEDs that do not allow delivery of more than 1 mW in the brain.

Cobolt MLD 473 nm used for excitation of opsins used in behavioral change studies of mice as they explore, and a rat experiencing reward. Courtesy of Cobolt.

“Before the development of optogenetic tools, we did not know within complex and tangled neural circuits which specific cells or brain regions were necessary for seizures,” Paz said. “Optogenetic techniques allow us to do what we have never been able to do earlier. This technology opens the door to a new era that will allow us to understand which cells to modulate and how to modulate them in order to treat various brain disorders without side effects.”

While both lasers and LEDs can be used as light sources to deliver specific wavelengths of light to brain tissue, the noncoherent light emitted by LEDs makes effective transmission of light difficult when coupling into the small core fibers required for in vivo rodent stimulation.

In an article published in January 2015 in the *Journal of Visualized Experiments*, Deisseroth and his team described two basic laser configurations that delivered particular wavelengths of light in deep brain structures of awake, freely moving rodents. The first was a single laser system that is precoupled by the manufacturer for an essentially ready-to-use approach — the only drawback being that the user is constrained by minimal end-user configuration.

The second was a dual laser system that enabled delivery of two different wavelengths along the same fiber. This, the team said, will become increasingly important in future experiments when different wavelengths will be used to activate or inhibit different cell types that are located close together.

DPSSLs

In the experiments, one of the lasers used was a 100-mW DPSSL from Cobolt that emitted yellow/orange light at a wavelength of 594 nm. For yellow/orange light in particular, today's LEDs lack the power to perform reliable optogenetic stimulation. However, yellow/orange DPSS lasers are extremely sensitive and the team found that they may behave erratically with reduced life span if rapidly modulated by a pulse generator.

It's true that direct modulation of a DPSSL, designed to run in CW mode, can result in erratic behavior, so vendors have worked hard to design a solution for the optogenetics community to meet the modulation requirements of fast rise time, repeatable pulse energy and long laser lifetime. In comparison, direct modulation of diode lasers (typically 473 nm) is more easily achieved.

Given this, Cobolt said its aim is to try to make it easier for optogenetics customers by providing a one or two laser line solution — either DPSSLs or diode lasers — including all the necessary beam combining and fiber coupling optics so the customer just needs to provide their modulation signal.

"In the case where a 594-nm DPSS laser is requested, then we integrate either a mechanical shutter or acoustic optical modulator and the DPSSL into one small box so the customer only needs to provide the modulation signal," said Elizabeth Illy, director of marketing. "New developments also mean that we can now offer directly modulated DPSSLs at 561 nm, which can meet the expectations of the optogenetics community. Our goal is to supply a compact solution that will deliver light in precisely the way the customer wants it, irrespective of which opsin they are using."

While lasers have traditionally been the go-to light source for optogenetics research, LEDs are gaining ground despite often being far less powerful.

"Lasers have high power and good beam characteristics but are expensive compared to LEDs," Illy said. "Even though LEDs have lower power, they are cheaper, flexible and can easily be modulated. It really comes down to what works best for the customer's particular experiment."

Implanted LEDs gain ground

It's true that lasers are more powerful and have thus far contributed significantly to a better understanding of the neural circuits pertaining to behavior, but thanks to the small size of an LED, it can be placed at the site of optogenetic stimulation. That means less power is required, among other benefits.

Lasers often require two or more optical fibers to connect the laser to an opsin — a light-sensitive protein. At each of these connections, power is lost, which means a higher starting power is needed. Another downside to utilizing fiber optic cables when studying the behavior of an awake mouse is the restriction placed on the animal's natural movements. And when it comes to experiments on multiple mice interactions, it's no surprise to learn that the cables quickly become tangled when more than one animal is on the move.

In a bid to free the animals and allow them to behave completely unimpeded, Mark Rossi at the Department of Psychiatry, University of North Carolina at Chapel Hill, N.C., and colleagues tested a wireless LED system that can be used to illuminate any brain area in a mouse. Thanks to a combination of a wirelessly controlled interface and a small implantable LED, the team found it could elicit movements reliably in the mice using a series of high-power stimulations without impeding natural movements.

“LEDs are gaining ground in optogenetics research because they are generally lower in cost than lasers and are small enough to be either carried by the animal research subject or implanted directly into the tissue of interest,” Rossi said.

“I have used both lasers and LEDs for behavioral neuroscience research, and each has its own value in the lab. I prefer to use lasers for experiments in which the mouse is stationary. Implantable LEDs allow wireless optogenetic stimulation, so I prefer LEDs for experiments involving unrestricted movement or social interaction.”

While Rossi believes that LEDs will permit a more thorough deconstruction of the neural circuits that contribute to social behavior, he points out that the biggest challenge is to develop an implantable LED that is powerful enough to sufficiently stimulate tissues and that can be remotely triggered.

“My biggest complaint with lasers is the cost and the longevity — a typical laser costs a few thousand dollars and will inevitably decline in performance (power, consistency),” he said. “LEDs may prove to be a cheaper, reliable light source. It would be helpful to have cheap, implantable LEDs that can be triggered remotely.”

In another wireless approach, assistant professor Mitsuhiro Hashimoto and colleagues at Fukushima Medical University in Fukushima, Japan, developed an LED stimulator capable of driving three independent LEDs upon reception of an IR signal generated by a custom-made IR transmitter.

Challenges for LEDs

The greatest challenge with going wireless, however, is the issue of the energy source. For sustaining experiments a large battery is needed, but for a small animal this added weight can obstruct head movement. For Hashimoto, wireless energy transfer would be extremely useful for optogenetic research.
“Unfortunately, it is difficult in Japan to use a wireless energy transfer with high power and a long distance, because it is not permitted by law,” he said.

The battle between LED and laser will continue with advantages and challenges facing both types of technology. For example, in the future, organic LEDs could replace lasers for brain mapping on freely moving animals thanks to developments in flexible organic LEDs. Wireless implantable LEDs that are powerful enough for a chronic treatment of brain disorders would also be critical in the future.
“For example, a closed-loop control of seizures with wireless LED devices that could disrupt a seizure with LED activation in real time at the onset of an automatically detected seizure would be a major advancement in the field — a challenge that we need to overcome,” said professor Paz.

On the other hand, new ultraminiaturized RGB laser modules could spell a future where lasers could be small and light enough to be mounted onto the head of a freely moving animal.