Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Integrated optoelectronic microprobes

L Rudmann, MT Alt, D Ashouri Vajari and T Stieglitz

Optogenetics opened not only new exciting opportunities to interrogate the nervous system but also requires adequate probes to facilitate these wishes. Therefore, a multidisciplinary effort is essential to match these technical opportunities with biological needs in order to establish a stable and functional material-tissue interface. This in turn can address an optical intervention of the genetically modified, light sensitive cells in the nervous system and recording of electrical signals from single cells and neuronal networks that result in behavioral changes. In this review, we present the state of the art of optoelectronic probes and assess advantages and challenges of the different design approaches. At first, we discuss mechanisms and processes at the material-tissue interface that influence the performance of optoelectronic probes in acute and chronic implantations. We classify optoelectronic probes by their property of delivering light to the tissue: by waveguides or by integrated light sources at the sites of intervention. Both approaches are discussed with respect to size, spatial resolution, opportunity to integrate electrodes for electrical recording and potential interactions with the target tissue. At last, we assess translational aspects of the state of the art. Long-term stability of probes and the opportunity to integrate them into fully implantable, wireless systems are a prerequisite for chronic applications and a transfer from fundamental neuroscientific studies into treatment options for diseases and clinical trials.

Address
Laboratory for Biomedical Microsystems, Department of Microsystems Engineering – IMTEK & BrainLinks-BrainTools Center, University of Freiburg, Georges-Koehler-Allee 102, 79110 Freiburg, Germany

Corresponding author: Stieglitz, T (stieglitz@imtek.uni-freiburg.de)

Current Opinion in Neurobiology 2018, **50**:72–82

This review comes from a themed issue on **Neurotechnologies**

Edited by **Luo** and **Anikeeva**

https://doi.org/10.1016/j.conb.2018.01.010

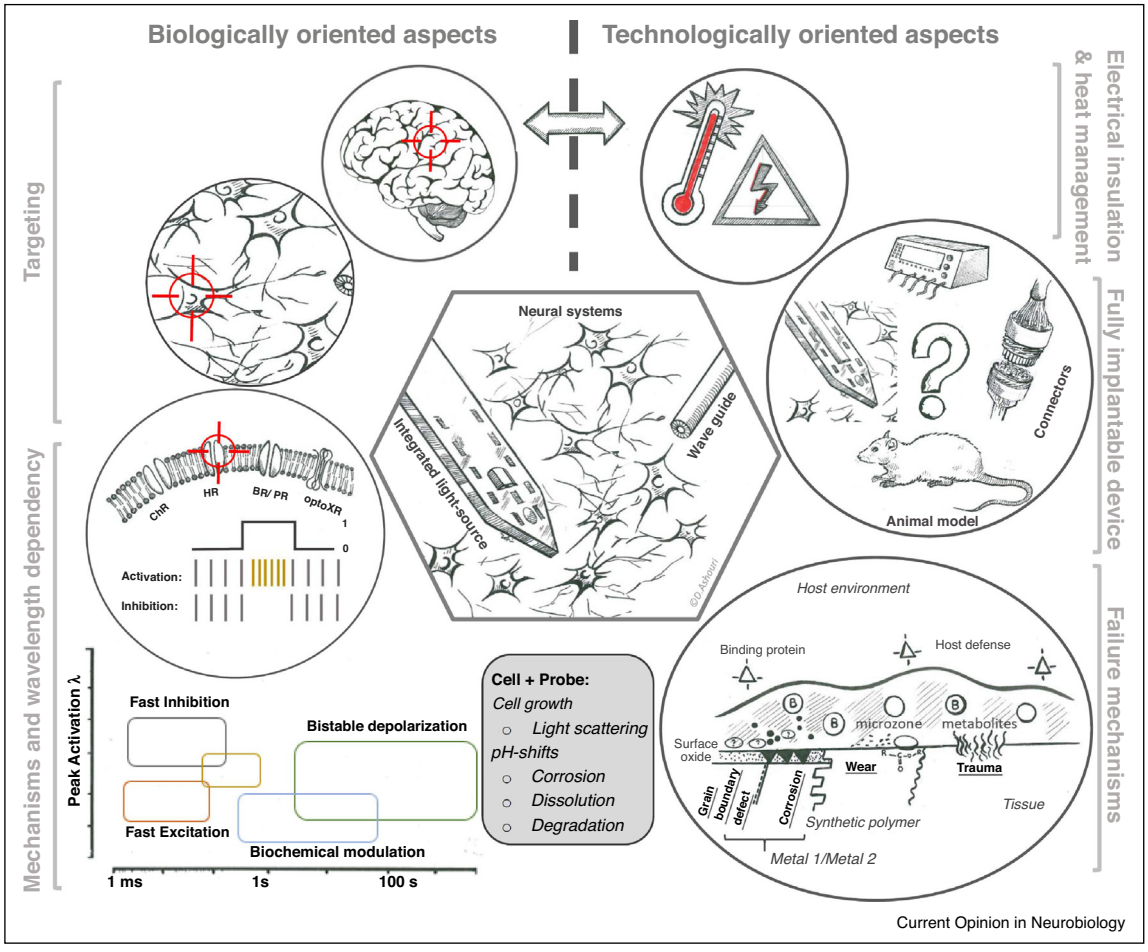
Introduction

Optoelectronic devices have entered our daily life over the last two decades in consumer electronics, communication, automotive and medicine. The knowledge about the possibilities of optogenetics to investigate the nervous system and gain better understanding of fundamental mechanisms in the brain spread from neuroscientists to other disciplines at latest when it was announced the "Method of the Year" in 2010 [1]. Optogenetics is a great tool to specifically target nerve cells that enables deep studies of detailed cell activity and even neural network connectivities. This is due to the injection of light sensitive ion channels so called opsins, extracted from algae or bacteria, into the target tissue. Thus, usage of different wavelength-dependent opsins facilitates optical stimulation or inhibition of distinct nerve cell activity. In contrast to sole electrical stimulation, where the surrounding electrode tissue is also affected by the stimulation, optogenetics allows a high target cell specificity. Microsystems engineers got aware that they might be able to develop powerful and sophisticated systems to optically stimulate genetically modified nerve cells. In those days, glass fibers as waveguides were the standard tool to excite the target tissue [2]. A plethora of papers has been published in the last years that presented ideas to miniaturize implantable probes, integrate waveguides on shafts [3••,4•,5,6••] with multiple recording sites [3••,6••] and assemble LDs (laser diodes) [3••,7] or LEDs (light emitting diodes) [8–10] directly on the substrate. Furthermore, the function of these devices has been demonstrated in either acute settings or implantations over a restricted time of weeks to some months [3••,4•,11–14]. In a nutshell, our review wants to complement the existing publications by a summery how the target application influences the design of integrated optoelectronic probes as well as advantages and limitations of different designs. Consecutively, we point out the engineering challenges which have to be taken to ensure longevity of implanted probes that eventually allow translational research studies toward human applications from the technical point of view.

Factors influencing optoelectronic probe design and performance

The neuroscientific research questions should always drive the engineering side of the probe design. If engineers understand these questions and needs and neuroscientists the possibilities and limitations of technology (Figure 1), a fruitful collaboration can get established. This might result in optoelectronic probes that meet the requirements to get answers to the research questions that have been asked. The intended implantation site of an optoelectronic probe determines the final device design. Accordingly, experts can derive the target specifications for substrate materials, for components to deliver light and record neural signals and for the final system concept (Box 1). The choice of the target area for transfection, the density and the volume of the nerve cell population to be

Figure 1



Framework of biological and technical interactions in optogenetic applications between the neuronal target tissue and the miniaturized optoelectronic probe.

Optoprobe devices for neural systems (center): the miniaturized integrated optoelectronic probes, mostly called optoprobes, translate the biological requirements into technical target specifications. The shape is adapted to the desired application and fiber-based or integrated waveguides on electrical recording arrays or integrated light sources (LDs or LEDs) are assembled on recording arrays. Either surface arrays or penetrating shaft designs dominate in cerebral studies while cuffs are favorable for peripheral nerve applications. Independent of the detailed design, all of the approaches share the same technologically oriented aspects and challenges. Biological and technological aspects influence probe design and performance on different levels. **Targeting:** the neuroscientific research questions determined the target region of interest in the brain, the peripheral nervous system and single-neuron as well as the population of neurons that shall be genetically modified. **Mechanisms and wavelength dependency:** different types of genetic vectors are available that allow activation or inhibition of nerve cells after optical stimulation. ChR: Channelrhodopsin, HR: Halorhodopsin, BR/PR: Bacteriarhodopsin, optoXR: genetically encoded optical tools. Peak activation wavelength of the opsins spanning the whole visible range from blue to red and optical excitation properties from the millisecond to the hundred second range result in fast excitation or inhibition, respectively, biochemical modulation and bistable depolarization [60]. **Electrical insulation and heat management:** implanted light sources need power supply that causes increased temperature due to power dissipation and current and voltage lines and contact pads have to be properly insulated to prevent undesired electrical stimulation of the nerve cells, electrolysis of water, redox reactions on organic molecules and pH value shifts. Apart from these biological reactions, artifacts can occur in electrical recordings by cross-talk between voltage pulses and recording electronics as well as due to photoelectric effects of optical stimulation [18•]. **A fully implantable device:** if fully implantable optoelectronic devices are available, the size of the technical system and the animal model have to match. Mouse models are widespread but mice are quite often much too small for the offered technical devices. In rat models, the implantable part of the device is well size-matched to target in the brain but connectors, cables and extracorporeal lasers as well as recording setups have to be considered to set up experiments that the animals can still carry the load of the technical system with respect to 'freely behaving' test paradigms. The target tissue always recognizes the implant as foreign body and starts reactions to 'either eat the implant up or to wall it out' (according to Buddy Ratner's fundamental work on biomaterials). **Failure mechanisms:** potential failure mechanisms have to be identified and measures have to be taken to minimize the reactions at the material-tissue interface. The 'race for the surface' starts immediately after the implantation. The local trauma triggers the foreign body reaction. Binding proteins approach the surface and mediate the further steps of the host response. Metabolites of macrophages or astrocytes, respectively attack the surface of the implant. Enzymes try to crack the backbone of polymers and to dissolve it and to degrade glass and ceramic compounds. Irregularities in metals like grain boundaries are starting points of corrosion. Incorporation of hydrogen and oxygen into metal electrodes leads to increased intrinsic mechanical stress and can cause delamination of the layers. If the foreign body