Computer Generated Holograms for In-vivo Optogenetic Neural Stimulation

Anastasios Tsakas, Dimitris Ampeliotis, Dimitris Alexandropoulos
Department of Materials Science, University of Patras, Patras 26504, Greece
dalexa@upatras.gr

Abstract: A novel design method for the *in-vivo* optogenetic photostimulation of neurons is presented. The method accounts for the brain tissue scattering effects for the holographic illumination of neurons.

1. Introduction

The exciting field of optogenetics refers to well defined and targeted stimulation of neurons that are functionalized with light sensitive opsins [1]. The prospects that optogenetics offers for specified neuronal activity has been embraced by the research community as an efficient tool towards demystifying the brain operation. Indeed, the optogenetic method has the potential of stimulating a complex of neurons down to single neuron. This unprecedent specificity and spatial flexibility cannot be matched by other deep brain stimulation techniques.

There is intense research activity in all aspects of optogenetics from the opsin to light sources and detectors. One of the key challenges for establishing optogenetics in in-vivo studies is the development of efficient neuron illumination techniques that will meet specificity requirements at the lowest possible optical power delivery, thus minimizing unnecessary heating of the human brain tissue. Today, this criterion is only partially met; there are some in-vivo demonstrations that deliver LED light by means of an optical fiber [2], yet the brain area that the light is diffused is determined exclusively by the optical fiber characteristics, thus compromising specificity. On the other hand, well defined and controlled neural illumination is achieved with deflection of laser light from spatial light modulators that carry holographic phase masks. The latter expands the vast accumulated scientific and technological knowledge on digital holography and Fourier optics techniques to optogenetics. Already, there are impressive variations of the holographic neural illumination that include that are applied even in 3D [3]. However, holographic illumination has been applied only in-vitro. This is expected to one extent, as in-vivo, i.e. in the brain tissue, illumination leads to rapid loss of phase information that is detrimental for hologram reconstruction. In other words, there are no accounts in the present day optogenetics literature on in-vivo holographic neural illumination. Here we present a novel design method for optogenetic hologram phase mask in the form of Computer Generated Holograms (CGH) to overcome the phase information loss in the brain tissue, by applying a pre-compensation that accounts for light propagation in the tissue, thus paving the way towards in-vivo optogenetic illumination with holograms.

2. Design method in-vivo optogenetic illumination with CGH

Our CGH design procedure (Figure 2) consists of 1) an iterative optimization algorithm, 2) a tissue scattering model and 3) simulated optical system for optogenetic experiment conduction. Particularly, we implemented the Normalized Gradient Descent (NGD) [4] algorithm which finds a local minimum of a differentiable function by taking repeated steps towards the opposite direction of its gradient at the current point. However, the optimization algorithm requires the computation of the gradient of the cost function at the output of the considered optical path.

To overcome this challenge, we implemented in the forward propagation of the optimization algorithm a numerical model [5] based on the Beam Propagation Method (BPM), that simulates the scattering biological medium as a series of parallel planar layers of phase masks. Each layer of the numerical model corresponds to a different depth into the biological medium. The numerical model relates the macroscopic optical properties of the medium, such as anisotropy and scattering mean free path, and the statistical parameters of the subsequent phase masks. The simulated optical system (Figure 1), before propagation in the tissue, in our optogenetic experiments is a 2f setup and is described by Fourier Optics operators [6].

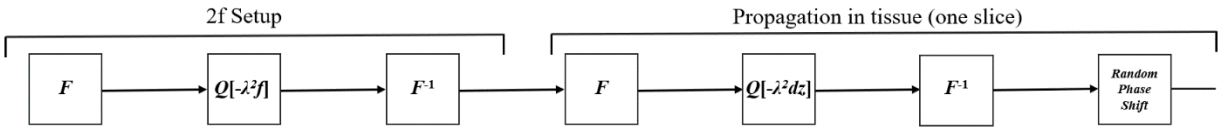


Figure 1: Fourier operators representation of the applied model

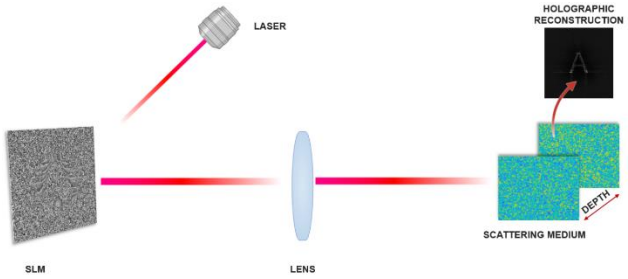
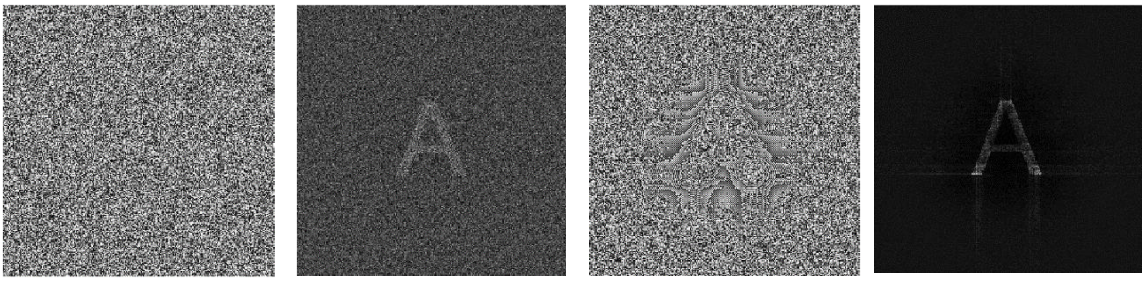


Figure 2: Schematic illustration of the simulated optical system

3. Results

We designed a CGH for the Alpha Letter using our proposed methodology for two specific cases. In the first case, we did not consider light propagation through brain tissue during the optimization procedure. As can be seen in Figure 3, holographic reconstruction at 40 um depth of brain tissue is strongly dominated by speckle noise. However, in the second case, NGD algorithm accounted for brain tissue scattering effects during CGH design process and as a result the holographic reconstruction at the same depth of tissue is speckle-free. It should also be noted that NGD algorithm converged to an optimal phase mask after 50 iterations for both cases.



(a) (b) (c) (d)

Figure 3: (a) Phase mask not accounting of brain tissue, (b) Reconstruction of the phase mask of (a), (c) Phase mask account of brain tissue, (d) Reconstruction of the phase mask of (c)

4. References

[1] "Method of the Year 2010," Nature Methods, vol. 8, no. 1, p. 1, Jan. 2011.
[2] A. M. Aravanis et al., "An optical neural interface: in vivo control of rodent motor cortex with integrated fiberoptic and optogenetic technology," J. Neural Eng., vol. 4, no. 3, pp. S143–S156, May 2007.
[3] E. Ronzitti, V. Emiliani, and E. Papagiakoumou, "Methods for Three-Dimensional All-Optical Manipulation of Neural Circuits," Front. Cell. Neurosci., vol. 12, 2018.
[4] S. Liu and Y. Takaki, "Optimization of Phase-Only Computer-Generated Holograms Based on the Gradient Descent Method," *Applied Sciences*, vol. 10, no. 12, Art. no. 12, Jan. 2020.
[5] X. Cheng *et al.*, "Development of a beam propagation method to simulate the point spread function degradation in scattering media," *Opt. Lett., OL*, vol. 44, no. 20, pp. 4989–4992, Oct. 2019.
[6] J. W. Goodman, *Introduction to Fourier Optics*. Roberts and Company Publishers, 2005.