2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

# Estimation of Retinotopic Map of Awake Mouse Brain Based upon Retino-Cortical Response Model

R. Togawa, M. Nakao, *Member, IEEE*, N. Katayama

***Abstract*— We proposed a novel retino-cortical response model on which the fine retinotopic map of the primary visual cortex was estimated from the intrinsic optical signal (IOS) induced by visual stimulation in an awake mouse. Our method was developed to overcome practical restrictions of measurement time and disturbances such as eye movement and brain background activity instead of synchronous averaging. In our model, it was assumed that the response of the cortical region was given by integrating the product of the image projected on a spherical retina and the retino-cortical sensitive function. In addition, in order to estimate parameters of the sensitive function, Monte Carlo-based numerical integration and nonlinear least square algorithm were employed. By applying this method to the actual IOS data, we estimated a biologically plausible spatial distribution of the sensitivity function parameters and a retinotopic map. Similar to our pervious study, higher-order brain regions such as the secondary visual cortex were also visualized. These results suggested usefulness of our proposed method based on the novel retino-cortical response model.**

***Clinical Relevance*— The method for evaluating visual functions under restoration was proposed and its validity was examined in animal experiments.**

## I. Introduction

Research and development of new prosthetic technologies such as artificial retina [1], iPS cells [2], and optogenetics [3] are underway to restore lost vision in humans. In this process, animal experiments using rodents and other animals are indispensable, but there is a problem that they cannot be used to test vision like humans. In order to investigate the process of vision recovery, long-term follow-up is necessary, but methods for this purpose have not been established.

Considering the possible influences of anesthesia on neurophysiological responsiveness and the burdensome of experiment on animals, it is desirable to be able to perform measurements in a short time without anesthesia. We have been studying on evaluation methods using visual field maps of the primary visual cortex measured using transcranial intrinsic optical signal (IOS) imaging [4]. This method has the advantage of being label-free and capable of recording cortical activity over a long period of time, making it easy to combine with various experimental techniques. However, the signal-to-noise ratio is intrinsically smaller than that of the exogenous optical signal imaging method [5][9]. In addition, during wakefulness without anesthesia, eye movements and pupil diameter fluctuations are more active, and the background activity of the brain is larger. In order to reduce their influences disturbing accurate estimate of the visual field map, we have recently developed the method estimating the fine retinal map based on the model of cortical sensitivity function underlying the regional response of the cortex to the stimulus image on the retina [6]. However, further sophistication of the model is needed to improve the accuracy of estimation.

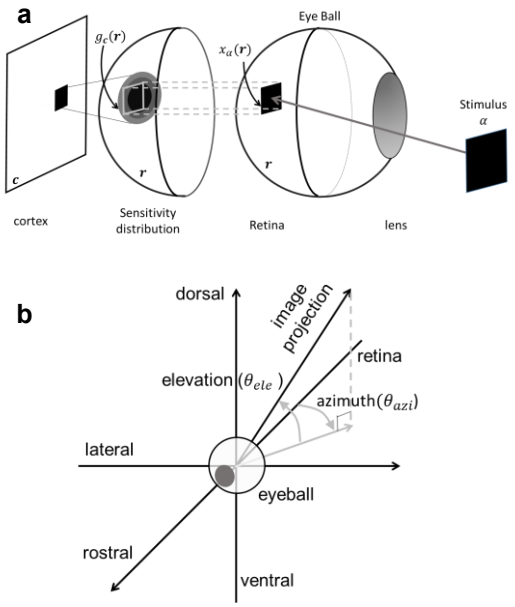


Figure 1. (a) A model of the retina-primary visual cortex system. (b) Definition of coordinate axes.

In this paper, we got the retinal space closer to the reality by representing it as a spherical plane, and re-defined the cortical sensitivity function on a polar coordinate system. Together with improvement of numerical computation, the model to enable estimation of a retinotopic map with much higher spatial resolution. By applying this method to the actual data, the usefulness of the proposed method was demonstrated.

## II. Methods

### A. Experiment Protocol

The experiment was conducted under the approval of the Animal Experimentation Expert Committee of Tohoku University. Since this study shared the data with our previous study [6], the experiment protocol was only briefly explained

*Research supported by JSPS KAKENHI Grant Numbers JP19K12773, JP20H04543, and JP19K08969 (for N. K.).

R. Togawa, M. Nakao, and N. Katayama are with Graduate School of Information Sciences, Tohoku University, Sendai, 980-8579 Japan (e-mail: nakao@ecei.tohoku.ac.jp). N. Katayama is also with Department of Humanities and Social Studies, Shoukei Gakuen University, Natori, Miyagi, 981-1295, Japan.

here. Two male C57BL/6 mice (10 weeks old and 11 weeks old) were used for the experiment. The mouse head was held on the experimental stage under no anesthesia, and placed under an epi-illumination microscope with a cooled CCD camera was placed under the microscope. A liquid crystal display was placed in the left visual field of the mouse and visual stimuli were presented. During visual stimulation, transcranial optical measurements of green scattered light (530-nm) in the right occipital lobe of the cerebral cortex were made [4] [9]. Simultaneously, the left eye of the mouse was photographed with an infrared camera. The method of Matsuda et al. was used for calibration of eye position and estimation of eye position and pupil diameter [8]. The visual stimuli ranged from 0° (frontal) to 112° (azimuth) and -35° to 45° (elevation) in the left visual field of the mouse. The screen was divided vertically at the height of the mouse's eye (0°) and further divided horizontally (37.3°, 94.6°) into three regions [4]. One of these six regions was randomly selected to display a grating pattern (10 different directions) with randomly changing angles every 0.6 s. A stimulus-free period of 8 s was interrupted after the stimulation of one region. Each region was stimulated 16 times (96 times in total) [4]. Experiments were conducted for three consecutive days, approximately one hour after the onset of the dark period. Data from the third day were used for analysis.

### B. *Preprocessing*

Since the power of noise, such as background activity in the brain, is approximately equal to the power of the evoked response signal, preprocessing to suppress the noise is necessary [4] [5] [9]. In fact, IOS contains very strong low-frequency fluctuations, which require a large amount of data (16-50 trials per stimulus location) to be removed by the synchronous averaging method [4]. Additionally, the fMRI and IOS signals contain a spatially synchronized low-frequency component called global signal (GS) [7], which is strongly correlated with heart rate variability [7], pupil fluctuation [9], etc. Therefore, we did the operation removing GS from local IOS as preprocessing [6][7]. This was expected to improve the signal-to-noise ratio without synchronous averaging.

### C. *Estimation of Retinotopic Mapping Based on Model of Regional Response of Cortex*

The response $\widehat{y_\alpha(\boldsymbol{c})}$ measured at ROI $\boldsymbol{c}$ in the cerebral cortex when presented with a visual stimulus α is modeled by the following equation (Fig. 1).

$$\widehat{y_\alpha(\boldsymbol{c})} = \int_{Retina} g_{\boldsymbol{c}}(\boldsymbol{r}) x_\alpha(\boldsymbol{r}) \mathrm{dS}(\boldsymbol{r}) \,, \qquad (1)$$

where $\boldsymbol{r}$ is the retinal polar coordinate, $x_\alpha(\boldsymbol{r})$ is the retinal image α (the luminance at position $\boldsymbol{r}$). The retinal polar coordinate system is shown in Fig. 1**b**. The assumption of spherical retina gets closer to the reality in comparison with the Cartesian coordinate system tangent to the fundus, which was used in the previous study [6]. Note that the flat retina assumption simplifies the calculation, but its error increases as distant from the center of the fundus. $x_\alpha(\boldsymbol{r})$ is calculated from the image and eye position. The sensitivity function $g_{\boldsymbol{c}}(\boldsymbol{r})$ of cortical region $\boldsymbol{c}$ against the retinal image at $\boldsymbol{r}$ was assumed as

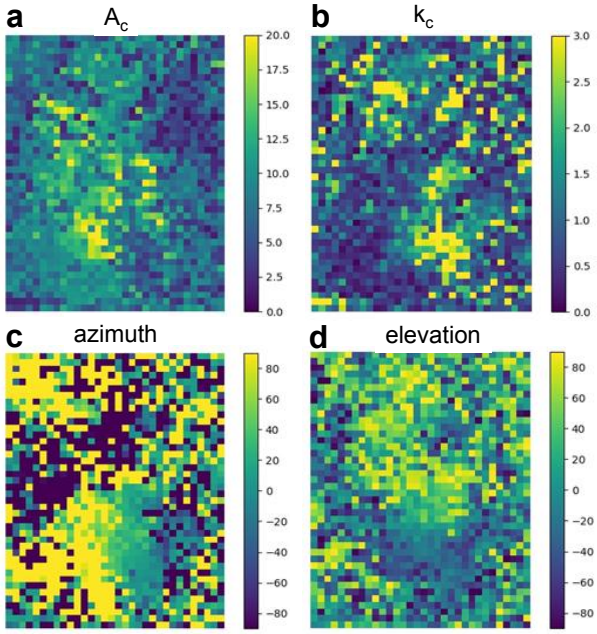


Figure 2. Estimation results of sensitivity function parameters of the cortex region. (**a-d**) Color-map representations of the parameters.

Von Mises–Fisher distribution function which is well known Gaussian-like function defined on a unit sphere [10].

$$g_{\boldsymbol{c}}(\boldsymbol{r}) = \frac{A_{\boldsymbol{c}} k_{\boldsymbol{c}}}{2\pi(e^{k_{\boldsymbol{c}}} - e^{-k_{\boldsymbol{c}}})} e^{k_{\boldsymbol{c}} \boldsymbol{\mu}_{\boldsymbol{c}}{}^T \boldsymbol{r}} \,, \qquad (2)$$

where $A_{\boldsymbol{c}}$ is a parameter characterizing magnitude of response, $k_{\boldsymbol{c}}$ parameter of the spatial extent of response, $\boldsymbol{\mu}_{\boldsymbol{c}}$ a central coordinate position of $g_{\boldsymbol{c}}(\boldsymbol{r})$ on the retina. This sensitivity function could be regarded to represent not only the direct retino-cortical projections but also the intracortical lateral connections. In order to estimate the parameters from the experimental data, the error function defined as:

$$f(A_{\boldsymbol{c}}, k_{\boldsymbol{c}}, \boldsymbol{\mu}_{\boldsymbol{c}}) \equiv \sum_\alpha \left(y_\alpha(\boldsymbol{c}) - \widehat{y_\alpha(\boldsymbol{c})}\right)^2 \,, \qquad (3)$$

and solve the constrained nonlinear minimization problem numerically: $arg \min_{A_{\boldsymbol{c}}, k_{\boldsymbol{c}}, \boldsymbol{\mu}_{\boldsymbol{c}}} f(A_{\boldsymbol{c}}, k_{\boldsymbol{c}}, \boldsymbol{\mu}_{\boldsymbol{c}})$ with the constraints, $A_{\boldsymbol{c}} > 0,\ k_{\boldsymbol{c}} > 0, \boldsymbol{\mu}_{\boldsymbol{c}} \in Retina$. The retinotopic map was estimated by placing the center of the sensitivity function, $\boldsymbol{\mu}_{\boldsymbol{c}}$, on the cortex. When (1) was numerically evaluated, Monte-Carlo integration was performed instead of time-consuming numerical integration by using $10^6$ point of retinal image.

## III. Results and Discussion

### A. *Parameter Estimation of Sensitivity Function of Cortical Region*

Estimated parameters of the sensitivity function of cortical region for the response signals with GS removed are shown for mouse 2 in Figs.2**a-d**. In this case, ninety six responses to the visual stimuli were used. As clearly seen from the retinotopic maps in Figs.3**a-c**, the responsive cortical area was located in the bottom half of the plot. Within this area, estimated position of the sensitivity function on the azimuth and elevation axes is shown to be gradually shifted horizontally and vertically, respectively. In addition, the magnitude $(A_{\boldsymbol{c}})$ and extent $(k_{\boldsymbol{c}})$

of sensitivity function were estimated to be smoothly distributed in a region-dependent manner. Since their estimation itself was done independently, the resulting smooth spatial distribution of parameters suggests stable and reliable estimation. With referring to the mouse brain atlas [11], it was confirmed that the estimated responsive area overlapped with most of the primary and secondary visual areas and some of the peripheral areas such as RSD, PtA, and the somatosensory cortex [6].

### *B. Estimation of Retinotopic Map*

The one-dimensional retinotopic maps obtained by smoothing the distribution of azimuth and elevation angles estimated by the proposed method are shown in Figs.3**a** and **b**. In this mouse, the azimuth angle had a peak value near the center of the extracted responsive area (about 80 degrees), and there was a folded structure in which the preference angle decreased in the medial and lateral directions. As for the elevation angle, it developed in the rostral and caudal directions. These topological features of the maps are similar to the previous study in which the flat retina was assumed [6].

The two-dimensional retinotopic map estimated by integrating azimuth and elevation angles is shown in Fig.3**c**. Although the estimated retinotopic map was significantly different from the reports measured under anesthesia [5], the topological features are mostly shared by our previous study in which the flat retina was assumed. Biological significance of finer difference remains to be clarified. As mentioned above, the medial part of the retinotopic map is likely to represent the secondary visual cortex. The structure of the higher-order visual cortex has not been reported by IOS imaging. In the future, it will be necessary to use electrophysiological methods to confirm whether this is indeed the structure of the secondary visual cortex.

## IV. Conclusion

We proposed a novel retino-cortical response model on which the fine retinotopic map of the primary visual cortex was estimated from IOS induced by visual stimulation in an awake mouse. In our model, it was assumed that the response of the cortical region was given by integrating the product of the image projected on a spherical retina and the retino-cortical sensitive function. In addition, in order to estimate parameters of the sensitive function, Monte Carlo-based numerical integration and nonlinear least square algorithm were employed. By applying this method to the actual IOS data, we estimated a biologically plausible spatial distribution of the sensitivity function parameters and a retinotopic map. The results suggested usefulness of our proposed method based on the novel retino-cortical response model. Further applications should be needed to quantitatively confirm the validity of our method.

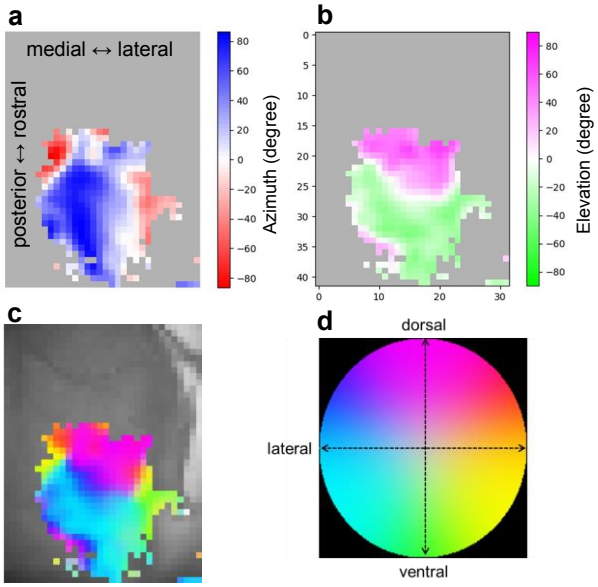


Figure 3. Estimated retinotopic maps of mouse 2. Contour plots of azimuth (a) and elevation (b) angles. (c) Two-dimensional retinotopic maps by the proposed method. (d) Color-code of the position on the spherical retina, where longitudinal ($\theta_{azi}$=0) and latitudinal ($\theta_{ele}$=0) lines are superposed.

## References


[1] E. Zrenner et al., "Subretinal electronic chips allow blind patients to read letters and combine them to words," Proc. R. Soc. B Biol. Sci., vol. 278, no. 1711, pp. 1489–1497, 2011.

[2] M. Mandai *et al.*, "iPSC-Derived Retina Transplants Improve Vision in rd1 End-Stage Retinal-Degeneration Mice," *Stem Cell Reports*, vol. 8, no. 1, pp. 69–83, 2017.

[3] H. Tomita *et al.*, "Restoration of visual response in aged dystrophic RCS rats using AAV-mediated channelopsin-2 gene transfer," *Investig. Ophthalmol. Vis. Sci.*, vol. 48, no. 8, pp. 3821–3826, 2007.

[4] D. Okuhata, N. Katayama, Y. Yoshida, and M. Nakao, "Development of quantification method of mouse visual ability based on brain imaging for assessment of visual restoration technology," *Proc. Life Eng. Symp. 2017, SICE*, vol. 2017, no. 1B3-03, pp. 0234–0238, 2017.

[5] J. Zhuang *et al.*, "An extended retinotopic map of mouse cortex," *Elife*, vol. 6, pp. 1–29, 2017.

[6] R. Togawa, D. Okuhata, Y. Yoshida, M. Nakao, and N. Katayama, "Estimation of the Retinotopic Map of an Awake Mouse Brain Based upon Intrinsic Optical," *Trans. Japanese Soc. Med. Biol. Eng.*, vol. 56, no. 4, pp. 157–163, 2018.

[7] Y. Yoshida, M. Nakao, and N. Katayama, "Resting-state functional connectivity analysis of the mouse brain using intrinsic optical signal imaging of cerebral blood volume dynamics," *Physiol. Meas.*, vol. 39, no. 054003, pp. 1–20, 2018.

[8] K. Matsuda, T. Nagami, Y. Sugase, A. Takemura, and K. Kenji, "A Widely Applicable Real-Time Mono/Binocular Eye Tracking System Using a High Frame-Rate Digital Camera," *Int. Conf. Human-Computer Interact.*, vol. 10271, pp. 593–608, 2017.

[9] M. A. Pisauro, N. T. Dhruv, M. Carandini, and A. Benucci, "Fast Hemodynamic Responses in the Visual Cortex of the Awake Mouse," *J. Neurosci.*, vol. 33, no. 46, pp. 18343–18351, 2013.

[10] G. S. Watson, "Distributions on the Circle and Sphere," *J. Appl. Probab.*, vol. 19, pp. 265–280, 1982.

[11] K.B.J Franklin, Paxinos G: The Mouse Brain. 2008.