別紙５（論文博士）

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Department: Electrical and Electronic Information Engineering			
Applicant's name 氏名	Lee You-Na	Contact faculty 紹介教員	Prof. Kazuaki Sawada

Abstract
論文内容の要旨（博士）

Title of Thesis 博士学位論文名	Image sensor technology for visualizing multi-neurotransmitters

(Approx. 800 words)
(要旨　1,200 字程度)

Recently the scientific studies of the nervous system have increased substantially with advances in analytical equipment. Those are wildly contributed it possible to understand how biochemical signals are transmitted through synaptic junctions by the release and the feedback of neurotransmitters. Their studies and the development of medicines require effective analysis equipment to quantify biochemical activities in neuronal communications and several analytical techniques have been developed. However, most of the analytical techniques focus on the detection of a single neurotransmitter, even though neurons communicate in a complex interaction of neurotransmitters. It led to the development of ISFET array based bio-image sensor which is portable and customizable as well as implantable for long-term recording. When comparing to neural probe arrays which are successfully applied to electrical signal recording in the brain, biochemical recording may be more complicated due to the diversity of neurotransmitters, but it is very encouraging by their similarity between the probe and ISFET arrays.

In this thesis, we will introduce a bio-image sensor which is ISFET based enzyme sensor array with integrated with readout in order to monitor spatiotemporal activities of various neurotransmitters in the same time.

This thesis consists of three main parts:

1. We invented new enzyme-immobilization technique using conventional photolithography. Before developing a bio-image sensor used for spatiotemporal monitoring of more than two neurotransmitters, we proposed an enzyme-immobilization technique that is the integration of an imaging device technology and ISFET based enzyme sensor. Using this technique, we can not only simply select the kinds of proton-consuming or-generating enzymes according to the neurotransmitters wishing to analyze, but also immobilize them in a planned shape on a pH image sensor by conventional photolithography technology. The prototype applying the suggested technique was fabricated and tested to image the concentration gradient of ATP and H^+. During the measurements, we became interested in H^+ diffusion via liquid, since the degraded ATP also by enzymatic reaction generates H^+ and the diffused H^+ were able to contribute to signal interrupting among neighboring pixels. When designing and placement of enzyme-immobilized pixels, the crosstalk by the H^+ diffusion should be considered to improve the target discriminability of a bio-image sensor.

2. We then applied this technique to fabricate ATP, ACh and H^+ image sensor as a further development of our previous research. This bio-image sensor contained a patterned enzyme-immobilized membrane, as small as a pixel size, to enhance spatial resolution. Moreover, several attempts, such as new pattern placements, barrier layers and microhole arrays, were attempted to reduce the H^+ diffusion via liquid. The fabricated bio-image sensors were demonstrated to confirm their multi-detection and discrimination abilities to visualize the concentration changes of ATP and ACh in real-time 2D images.

3. Additionally, we modified the circuit design of the pH-image sensor to improve spatiotemporal resolution in order to investigate the neural networking in detail. The pH image sensor was developed toward large-scale, high-density and fast frame rate imaging. The pH image sensor was fabricated by a modified CMOS process technology. A small pixel pitch was achieved by utilizing a shrunken in-pixel circuit and an efficiently arranged readout circuit architecture. Moreover, the frame rate was able to accelerate by operating steps of measuring and read out in parallel. We demonstrated the imaging capability with our evaluation method for practical high-spatial resolution in biological environments and compared the experimental result with the simulation result to figure out the reason then.