別紙４－１（課程博士（英文））

Date of Submission (month, day, year): January 8th, 2021

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Abstract (Doctor)

Title of Thesis	Development of a nanomechanical biosensor integrated with an optical interferometric transducer

Approx. 800 words

When a human being is infected by viruses or cells are exposed to stress, various molecules are released as a molecular pattern from the lesion site to the dendrites and macrophages, and their concentrations gradually change. The comprehensive detection of these biomarkers would enable patients with brain dysfunction and infections to be treated appropriately according to the progression of the disease and the probability of mortality and sequelae would reduce. A sensor that can detect a variety of molecules, from small molecules to macromolecules, regardless of molecular size, should be developed to detect these molecular patterns. Although various conventional semiconductor sensors have been developed, a sensor which can comprehensively detect molecules of various sizes in a biological environment without extending the Debye length has not been realized. The micro-electro-mechanical system (MEMS) optical interferometric surface-stress sensor proposed by our laboratory can comprehensively detect low-concentration and small molecules, which have been difficult to detect using conventional surface-stress sensors, as well as macromolecules exceeding the Debye length by optimizing the wavelength selectivity and geometry parameters of the interferometer. Therefore, for a highly sensitive detection of target molecules of various sizes, interferometers with metal half-mirror and cavity-sealed structures with optimized geometry parameters, which can improve the detection performance of the sensor, were fabricated and bio-interfaces for adsorbing molecules on the sensor were constructed. Through the above tasks, this thesis presents the development of the sensor for a label-free and comprehensive detection of proteins and neurotransmitters in liquids and gas molecules in air.

First, the MEMS interferometer with metal half-mirrors structure was studied. Assuming this device is used for blood inspection, Au was selected as the half-mirror material because it has a superior transparent characteristic in the near-infrared wavelength region, where the absorption coefficient of blood components is small. Subsequently, we fabricated a MEMS interferometer with Au half-mirrors and constructed a bio-interface onto the interferometer to immobilize the albumin antibodies. The chip was immersed in the solution and the response of the sensor was obtained when the sample containing the albumin antigen molecule was added at a final concentration of 10 ng/mL and when other proteins were added. As a result, only the former exhibited the deflection of the membrane, suggesting the possibility of selective detection of macromolecular proteins using the antigen–antibody reactions. Based on the results of this study, our research group constructed a MEMS interferometer with optimized geometry parameters and evaluated the concentration dependence and limit of detection (LOD) for macromolecular proteins. The results indicated that the sensor reacted in a low concentration range of 100 ag/mL–1 ng/mL, and the LOD was observed to be 100 ag/mL–1 fg/mL. The results indicated that this is the most sensitive detection of macromolecular proteins in label-free semiconductor biosensors.

In the early interferometers with metallic half-mirrors structure, the sealing of the interferometer was incomplete because of the constraints of the fabrication process. Therefore, a new interferometer with a cavity-sealed structure was studied. Considering the application of this sensor to the detection of both proteins in liquids and gas molecules, we proposed to use the polymeric material used as the

molecular adsorption layer of the proteins as a gas-reactive layer. Optical and finite element analyses of the newly proposed sensor were performed and an interferometer with optimized various parameters was fabricated. Subsequently, a polymer that functioned as a gas-reactive film was deposited on the interferometer, and the concentration dependence and minimum detection limits for volatile ethanol were evaluated. We observed that the linear response was acquired in the concentration range of 5–110 ppm, and the LOD was 5 ppm. The result indicates that the sensitivity of the sensor was comparable to semiconductor-based sensors, which have the highest sensitivity for measuring ethanol at room temperature; this suggested the feasibility of the sensor that can detect ethanol concentrations of sub-ppm by optimizing the geometry parameters of the interferometer.

Finally, to demonstrate the detectability of small molecules in the liquid, we studied the use of a molecularly imprinted polymer (MIP) as a molecular adsorption layer that can adsorb neurotransmitters. Considering the integration with the sensor, we used electrochemical polymerization to enable the selective formation of the MIP with the template of dopamine (DA), which is well known as a neurotransmitter, on a conductive material in liquid, and formed the MIP film. Subsequently, the sensor was immersed in phosphate buffered saline (PBS) and the time course of the reflection spectrum was acquired when the DA was added into PBS to bring the final concentration to 1 μM. As a result, the deformation of the deformable membrane was observed only in the presence of DA, and the spectral response owing to the adsorption of DA was acquired, suggesting the feasibility of detecting neurotransmitters.

In this study, we realized the label-free detection of proteins and neurotransmitters in liquids and gas molecules in air using the proposed sensor and demonstrated the feasibility of a sensor that can detect molecules of various sizes. We expect that the realization of the device that has no restriction on the size of detectable molecules and can measure the adsorption process of target molecules in real-time will become an innovative basic technology in medical research.