別紙４

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主 論 文 の 要 旨

論文題目　Identification and analysis of functional neural circuits that regulate behavioral strategies for thermotaxis in the nematode *Caenorhabditis elegans*

(線虫 *Caenorhabditis elegans* の温度走性を実現する行動戦略の同定，およびその神経回路基盤の解析)

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論 文 内 容 の 要 旨

In attempts to understand how the brain works, neurobiologists have been deducing sets of neurons and brain regions that are involved in a brain function. Over the past centuries, anatomical and clinical studies have provided such information by showing relations between brain damage and impairment of functions, helping to investigate involvement of each of the brain regions. Electrophysiological studies have revealed how the brain encodes sensory input and decodes motor output. In the 21st century, connectome projects have been launching all over the world, aiming to describe complete anatomical wiring diagram and decipher neural pathways for producing a function. These projects rely on brain-wide imaging approach such as fMRI for human and fluorescence imaging for rodents. However, recent imaging studies show that the nervous system is dominated by task-unrelated activity evoked spontaneously or by task-unrelated movement. The fact that the nervous system is filled with uninstructed activity distresses imaging-based functional mapping of neurons and brain regions.

In this thesis, I propose an approach to identify functional neural circuits. I employ the nematode *Caenorhabditis elegans* which provides complete wiring diagram at synaptic scale. Also in *C. elegans*, anatomical and ablation studies have provided information about neural contributions and revealed several sets of neurons that mediate a function. However, these attempts have been struggling to describe complete neural pathways —from sensory to motor neurons—, and moreover, several studies have indicated drastic disparities in neural contributions to *C. elegans* brain functions, one of which is thermotactic behavior. *C. elegans* can sense and memorize the environmental temperature in association with the presence of food and migrate toward that cultivation temperature when placed on a thermal gradient without food. This memory-dependent navigation behavior lacks a consensus of its underlying neural circuits. Here, I show that the discrimination of environmental contexts (relative differences between the currently experiencing temperature and the past cultivation temperature) is a critical step to identify neural circuits and dissolve the disparities in the previous studies. I overcome the incompleteness of functional mapping by performing population analysis with high-resolution behavioral recording and large-scale single cell ablation and silencing. Further, I find that robustness and flexibility in the nervous system, which has prevented the identification of complete neural pathways, can be overcome by subdividing *C. elegans* behavior into behavioral components: turns, reversals, and curves. My simulation analysis suggests that regulation of curves, namely steering behavior, plays the most prominent role in thermotactic migration.

I next propose two approaches to decipher information processing within the identified neural circuits. Firstly, I perform calcium imaging analysis in freely-moving and immobilized *C. elegans* animals and find that sensory neurons and a first-layer interneuron in the circuits show context-dependent information processing, thereby consistently navigating animals to their cultivation temperature under the different environmental contexts: below or above the cultivation temperature. Secondly, I perform modeling analysis in which the identified sets of neurons that mediate steering behavior are mathematically represented. Unknown parameters in the model are determined by running evolutionary searches, so that the model reproduces empirical thermotactic migration and steering behavior. I find that the model generates steering not upon sinusoidal thermal input during dorsoventral head swings of animals, as previously proposed, but upon more persistent thermal input during forward movement. Consistent with this, decomposition analysis on neural activity depicts information flow from a sensory neuron to motor neurons at longer time scale than the dorsoventral oscillation.

Considering the recent progress in neurobiology, the proposed approach for identifying functional neural circuits which relies on complete wiring diagram and large-scale cell intervention would soon become applicable to other model animals. Other than mathematical decomposition which is employed in this study, statistical mechanics, information theory, and network theory can be breakthrough approaches for analyzing neural activity data of the circuits. I claim that such holistic feature extraction from high-dimensional activity data will be a next step of the connectome projects. As shown in this thesis, *C. elegans* provides unique opportunities to assess the validity of diverse approaches by its abundant information and prominent manipulability, leading us to solve the mystery of our brain: cognition, emotion, and consciousness.