【Grant-in-Aid for Scientific Research (S)】

**Broad Section G**

**Title of Project : Spatio-temporal variabilities and robustness in pre-implantation mammalian development**

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## 【Purpose and Background of the Research】

Living systems exhibit variabilities in space and time, such as cell shape, tissue size, and the timing of cell division and differentiation. Nevertheless, they robustly establish an order and function as a whole. Determining how living embryos develop a defined form and function at the right time despite the inherent variability remains a fundamental question in biology.

In this study, we aim to understand the design principles of robustness and self-organization using early mammalian embryos as a model system. We applied quantitative, physical and mathematical approaches and proposed a model in which multi-scale feedback regulation is a key for self-organization of tissue shape and pattern (Figure 1). We will further develop our interdisciplinary method and model to elucidate the interplay between spatial and temporal regulations as well as the relationship between variability and robustness. Furthermore, we will explore mechanisms shared or distinct across mammalian species. This study will form a basis for mechanistic understanding of human development.

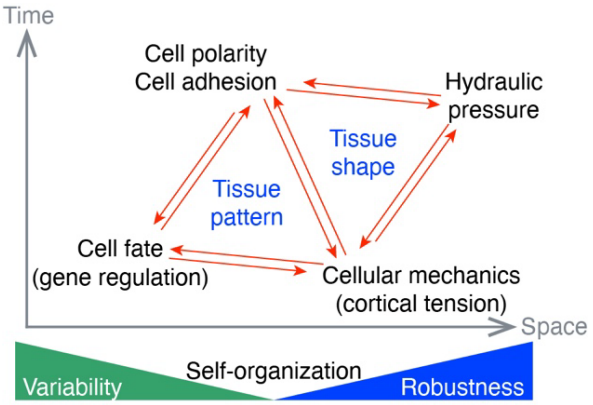


**Figure 1. Self-organization in living organisms.** Multi-scale feedbacks interact across space and time to achieve robustness in the living system.

## 【Research Methods】

We will measure 1) spatial variabilities of cell shape, cell-cell interactions and tissue architecture during embryonic morphogenesis, and 2) temporal variabilities such as the timing of cell division and lineage segregation. These measurements will then be 3) integrated into a map to investigate their possible relationship and role in robustness. We will then apply our findings to 4) explore possible mechanisms of embryo size control. Finally, we will 5) identify interspecies conservation and differences in self-organization mechanisms using monkey embryos as a model of humans.

## 【Expected Research Achievements and Scientific Significance】

The present study addresses a fundamental question in biology. With their regulative capacity, early mammalian embryos are an ideal system to address this question. Our quantitative and interdisciplinary approach will bring in a breakthrough.

The insights and technology obtained in this study can form a basis for our understanding of human biology. Given the recent interest in developing systems mimicking the robustness of living systems, such as neural networks, understanding the robustness principle will contribute to developing further diverse technologies.

## 【Publications Relevant to the Project】


- Maître, J.-L., Turlier, H., Illukkumbura, R., Eismann, B., Niwayama, R., Nedelec, F. and Hiiragi, T.: Asymmetric division of contractile domains couples cell positioning and fate specification. **Nature** (2016) 536(7616), 344–348.
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- Chan, C.J., Costanzo, M., Ruiz-Herrero, T., Mönke, G., Ryan, P., Bergert, M., Diz-Muñoz, A., Mahadevan, L. and Hiiragi, T.: Hydraulic control of mammalian embryo size and cell fate. **Nature** (2019) 571(7763), 112-116.


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