【Grant-in-Aid for Transformative Research Areas（B）】

# A unified science of "life/non-life transition" encompassing cells and artificial cells

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## Purpose and Background of the Research

### ●Outline of the Research

What is the fundamental difference between something that is “alive” and something that is “dead”? It is as clear as day that a pebble by the roadside is non-living, while the cat walking past it is alive. But what distinguishes a cat[1)] that has just died from the same cat that was happily running around moments before? Because very little time has passed since death, the molecular makeup of its body remains virtually unchanged, making it hard to tell life from non-life based on components alone. What actually changes when a living creature becomes dead? By combining expertise in microbiology, artificial-cell research, mathematical modeling, and computational complexity theory, we seek to uncover exactly how this transformation occurs—and, in doing so, to establish a new discipline: the science of the life–nonlife transition.

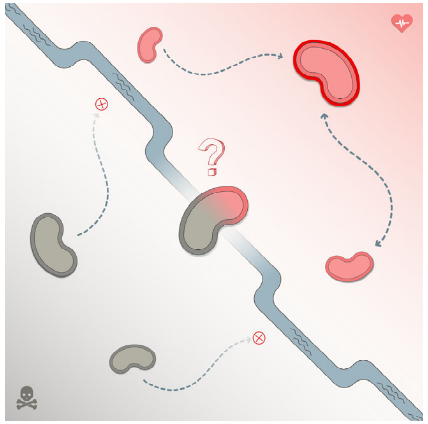

Figure 1. A conceptual figure of the life–nonlife transition. The upper-right region represents the “living” state of a cell, while the lower-left shows its “dead” state. The boundary separating these two regions—evocative of the River Styx—is termed the “life–nonlife transition boundary,” which we aim to elucidate. (Illustration by I.D. Urushibata)

### ●Multimodal Approach Encompassing Natural Cells and Artificial Cells

To extract the essence of “life” versus “death” in as general a form as possible, this research area investigates not only living cells but also chemically synthesized “artificial cells.” While traditional studies of cell death have meticulously characterized the key signaling molecules involved, our focus is not on species-specific differences but on the phenomena that universally occur during the death process of any living system—including artificial cells.

1) The cat is used merely as an illustrative example and is not an experimental subject in this research. This project focuses on the cell death of unicellular organisms, not the individual death of multicellular life.

## Expected Research Achievements

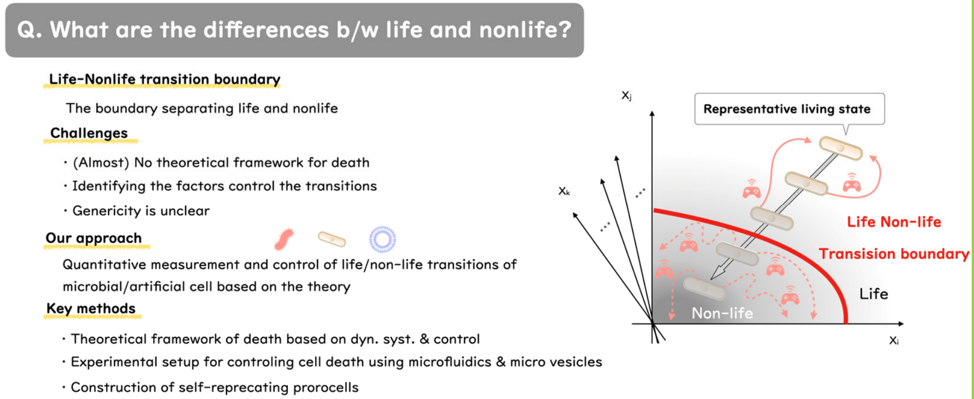


Figure 2 The questions, research plans, and key methods

### ●Research Plans

<u>A01: Analysis of the Universality of Cell Death</u>

We comprehensively analyze how Escherichia coli and yeast respond at the molecular level when subjected to various lethal stresses. For example, we measure global shifts in protein and metabolite profiles during the dying process rather than focusing on individual molecules. From these data, we ask whether there are multiple distinct “modes” of death or whether different causes lead to similar death dynamics, thereby probing the universality of the cell-death process.

<u>A02: Quantifying the Life–Nonlife Transition Boundary and Cellular Revival</u>

Building on our proposed “definition of death”—that a cell is alive if we can steer its gene-expression state back to a representative “living” point, and dead otherwise—Team A02 will experimentally determine the life–nonlife transition boundary in E. coli. We will then perform revival experiments that deliberately cross this boundary in reverse to resurrect cells.

<u>B01：Theoretical Framework for the Difficulty of “Creating Life”</u>

To date, no one has achieved de novo chemical synthesis of a living system. This likely reflects the extreme challenge of “building life” from scratch—though we cannot exclude the possibility that it may prove simpler than expected once accomplished. Team B01 will combine computational complexity theory, which quantifies problem difficulty, with von Neumann–style theories of self-replicating systems to develop a theory explaining why creating life is so hard.

<u>B02：Analysis of the Death Process in Artificial Cells</u>

Artificial cells are chemically assembled entities endowed with self-production capability. While natural cells have divided continuously for about 3.8 billion years, artificial cells still fail to sustain long-term division and eventually lose their self-production during experiments. We will elucidate the chemical changes that accompany this loss of self-production, identifying the conditions that terminate this vital life function and seeking ways to extend the maximum number of divisions.

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| Homepage Address, etc. | Website of PI: https://www.yhimeoka.com<br>Website of the project: Under construction |