Research area in Strategic Objective *"Discovery and exploration of unknown biological response mechanisms"*

Multiscale and interdisciplinary approaches to investigate mechanisms of resilience and diversification across wide ranges of spatiotemporal metrics

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Overview

The focus of this research area is on the dual nature of organisms' responses, resilience and diversification, across a wide range of spatiotemporal metrics, with the aim of elucidating and eventually controlling their underlying mechanisms through the optimization and development of multiscale and cross-disciplinary techniques.

Biological phenomena occur across a large range of spatial scales, from molecules to tissues, individuals, and populations; they are also variable with regard to temporal scales, as represented by fast chemical reactions in cells or the lifespan of individuals, extending to transgenerational effects. Within this vast spatiotemporal world, although organisms respond to external stimuli over time, they resist or recover from such perturbations (resilience). They may also chance to attain a distinct, stable state that differs from the original state (diversification). Collectively, these organisms' responses are considered as "biological potentials" in this research area.

In order to elucidate the mechanisms of resilience and diversification, it is critical to clarify the causal relationships among biological phenomena across large spatiotemporal scales. Therefore, it is necessary to construct appropriate quantitative methods by combining and/or optimizing existing techniques or even developing new ones, depending on the modality of information to be obtained and the amount of data to be collected. Currently, the recent advancement of omics and other technologies has made it possible to acquire large amounts of complex data at individual coordinate points in space and time. Thus, informatics approaches will be indispensable to leverage individual as well as multiple data sets to comprehend their biological significance.

By cycling measurements, data analysis, hypothesis formulation, and verification, this research area aims at elucidating the mechanisms that shape biological potentials in various contexts. Moreover, this research area will uncover previously overlooked biological potentials.

Research Supervisor's Policy on Call for Application, Selection, and Management of the Research Area

1. Aims of this research area and examples of research and development

Organisms are exposed to external stimuli and internal changes throughout their life cycles. These encompass unsettled climates and diets, infections by pathogens, and qualitative and quantitative changes in tissues and biomacromolecules over the passage of time. Although such stimuli and changes often result in growth retardation and/or decreased reproduction, organisms are able to buffer such effects within certain bounds (resilience). On the other hand, because those stimuli and changes are heterogeneous throughout a tissue or a population, no cell within a tissue or no individual life history within a population is strictly invariant, and such variations may chance to be stabilized (diversification), transmitted beyond generations, and lead to environmental adaptation and evolution. This research area aims at dissecting and controlling the mechanisms underlying the above dual nature of "biological potentials." The goal of this basic research, once achieved, is expected to provide scientific bases for the prevention of diseases, extension of healthy life spans, and innovations to primary industries that contribute to the achievement of a sustainable society.

Numerous biological phenomena extend across large spatiotemporal scales, and some of these phenomena may be causally linked to the resilience or the diversification of interest. The more distantly such phenomena are located from each other, the more challenging it will be to demonstrate the causal relationships among those and to uncover the enigmatic mechanisms that link them. As such, this research area welcomes proposals that attempt to connect the phenomena beyond scales; for example, scales ranging from molecules to complete plants or animals, at the least, or scales ranging from single microbes to microbial populations, and on to interspecies interactions between microorganisms and symbiotic plants or animals in communities of diverse species. With regard to the resilience and the diversification in this research area, the concept of resilience includes suppression and prediction of functional decline or recovery from diminished function at the individual or population level, whereas the concept of diversification includes differences in traits among individuals in a population, among strains within a species, and among species. This research area encourages applicants to submit proposals that are literally "scaled up" beyond their research in the past.

The progress of modern life sciences parallels the progress of technological innovations in collecting data with larger amounts of information, higher accuracy, and multimodality, with compatible tools to analyze those big data sets. In this research area, the development and implementation of such innovations will be one consideration in the selection process, evaluating how the applicants combine, optimize, and/or develop technologies for data collection and analysis to elucidate the mechanisms that shape biological potentials. However, it should be emphasized that this

research area does not invite proposals for technological innovations only, without including an approach toward addressing the underlying biological mechanisms.

The following are examples of research foci, combinations of phenomena, and technological developments consistent with the scope of this research area, all of which are just the tip of the iceberg and should be considered as limited points of reference to help the applicants' understanding.

(1) A proposal to measure the response to multimodal stress over time and to identify the hidden mechanisms behind the trade-off between growth and reproduction, with a goal to find ways to minimize the decline in reproductive fitness provoked by the multimodal stress.

(2) A proposal to employ interspecies comparative approaches by using conventional model organisms and their closely related non-model species that show significantly different adaptive capacities, with a goal to optimize the adaptation.

(3) A proposal to monitor turnover of cells in a less well-characterized tissue by developing a tool to visualize stem cells from developmental stages to old age, highlighting the maintenance of stem cell function in aged individuals and raising the possibility of controlling individual aging.

(4) Development of technologies to measure the amounts of multiple metabolites at the organelle level, to address how changes in nutritional status affect metabolism in individual organelles, elucidating the causal relationship between such local metabolic changes and effects on tissue- and individual-level traits.

(5) Development of devices that automatically monitor disease progression or measure life span on a large scale to investigate the impact of lifestyle factors such as sleep and exercise, with an ultimate goal to predict disease susceptibility, progression, and remaining life by analysis of the acquired data.

(6) A proposal to construct an experimental system consisting of plants, animals, and symbiotic microorganisms, with the aim of evaluating the effects of genetic modification of specific microbial species, or changes in the composition of the microbial species, on the dynamics of the ecosystem from multiple perspectives, such as developmental timing and immunological capacity.

2. Notes on research proposals and management of the research area

(1) Materials employed in research may include microorganisms, fungi, plants, animals, viruses, and combinations thereof. Every effort will be made to select proposals that use a variety of materials as a whole.

(2) Proposals should be structured in a manner that is accessible to scientists outside the immediate fields. For example, the proposal should clarify the nature of the "biological potentials" to be explored, what is their importance, and how unique is the approach. The proposal should also

address the future possibility of collaborative work with researchers in other fields. Technical or conceptual terms and their abbreviations specific to the research subject should be clearly stated when they first appear in the proposal.

(３) Proposals not only for “short-term” goals but also for “long-term” goals will be considered for selection. The goals that can be completed within the research period are referred to as “short-term” goals here. Proposals for “long-term” goals, if approved, are expected to serve as the foundation for outstanding achievements beyond the funded research period.

(４) It is anticipated that this proposal will be conducted as the core research theme of the applicant once it is adopted. In the proposal, it should be clearly stated whether there are other projects that have been supported by other grants and funding, and how different this proposed research is compared to other funded projects. Excellent proposals that align with the concepts of the strategic goal and this research area ultimately may not be selected, regrettably, if they are already supported concurrently by major grants.

(５) This research area provides regular closed group sessions for awardees. These sessions are interdisciplinary platforms where young scientists, possessing distinct expertise, employing various techniques and raising their own original questions, discuss their research on biological potentials. We urge the awardees to prepare presentations for these sessions, taking the point of view of a broad audience, and to engage in constructive discussions as active audience members throughout the support period. To build such a motivated team, we will carefully survey proposals and conduct interviews.

We request that you fully understand the above notes before submitting your proposal.

3. Research period and research funds

The support period is three and a half years from the fiscal year of selection. Research expenses are up to 40 million yen in total (excluding indirect expenses). In the selection process, whether the research expenses are appropriately allocated in accordance with the content of the proposal will also be subject to evaluation. Research proposals conducted on a smaller budget scale are not excluded from the selection process.