博士論文の要約

論文題目：Design Principle of Information-Integration Structures in Biological Signaling Systems (生命のシグナル伝達システムにおける情報統合構造の設計原理)

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Living organisms integrate multiple signals to generate appropriate responses, enabling them to perceive their surroundings and act accordingly. Even at the single-cell level, cells integrate multiple extracellular inputs through signaling systems. For example, in many signaling systems, diverse extracellular inputs are funneled into a small set of hub molecules in the intermediate layer and are subsequently expanded into diverse downstream responses. Such "diverse input–few middle-layer (hub)–diverse output" structures are widely observed and commonly referred to as bow-tie architectures. Representative examples include the ERK, p53, and NF-κB signaling pathways. In the ERK pathway, for instance, distinct stimuli such as the differentiation factor NGF and the growth factor EGF are funneled into the phosphorylation of ERK, followed by the activation of diverse downstream targets (Fig 1**a**).

Despite their ubiquity, bow-tie architectures inherently pose a risk of information loss due to the bottleneck that compresses diverse inputs into the hub molecules. Nevertheless, the ERK, p53, and NF-κB pathways can preserve input specificity by encoding information in the complex temporal dynamics of hub-molecule activity, a strategy known as temporal encoding. For example, ERK exhibits sustained activation in response to NGF, whereas it often shows a transient pulse in response to EGF (Fig 1**b**). Through these stimulus-dependent temporal patterns, the ERK pathway can transmit input information even under the bottleneck constraints.

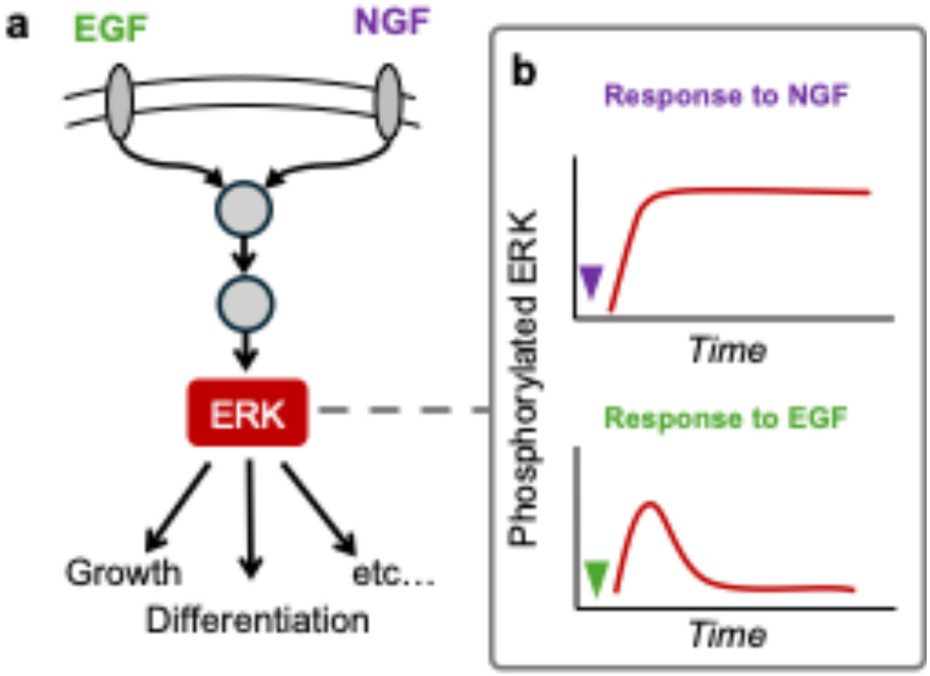

Figure 1. Input-information integration structure in signaling system (a) Schematic of the Ras–ERK signaling pathway. Diverse upstream inputs converge onto ERK and then excite proper program. **(b)** Input specific ERK activity dynamics. Different input-signals induce distinct ERK activation dynamics. These stimulus-dependent temporal patterns convey input information to downstream.

This structural-functional combination poses a seemingly paradoxical design: information compression (bow-tie integration) coupled with input-specific transmission via rich temporal dynamics (temporal encoding). This dissertation investigates mechanisms that give rise to this paradoxical design by combining evolutionary simulations, dynamical-systems analysis, and information-theoretic analysis.

In Chapter 2, I address the evolutionary mechanisms underlying bow-tie architecture. Previous studies have suggested that bow-tie architectures could be the result of selection for functional advantages (e.g., robustness, controllability, evolvability) or specific evolutionary goals (e.g., low-dimensional input–output mappings). In contrast, using evolutionary simulations and dynamical analysis of a hierarchical linear network model, I demonstrate that bow-tie architectures can emerge spontaneously as a byproduct of evolution, without being selected as an adaptive trait. When evolutionary adaptation starts from weak interactions, the multiplicative nature of mutations in molecular affinities amplifies small stochastic differences among interaction strengths, leading to pronounced heterogeneity in the intermediate layer and driving the formation of a narrow bottleneck. These results suggest that the bottleneck structures (bow-tie architectures) in extant signaling systems, including the ERK pathway, may have emerged without being directly selected for as an adaptive trait.

In Chapter 3, I investigate the conditions under which temporal encoding with complex temporal patterns emerges under the bottleneck constraints. Under such constraints, encoding information into hub molecule activity is a natural strategy for preserving multiple inputs. Intuitively, encoding information solely in activation amplitude might suffice. Nevertheless, real cellular encoding waveforms often exhibit complex dynamics, including pulsatile or transient responses, as exemplified by the ERK pathway. To identify when such complex temporal patterns are inherently required for information transmission, I develop an encoder–decoder framework that combines continuous-time state-space models with information theory. In this chapter, I first provide an operational definition of temporal encoding as the fraction of transmitted information carried by transient dynamics, giving a quantitative interpretation to temporal encoding that has been discussed

qualitatively. Combining evolutionary simulations, dynamical-systems analysis, and information theory, I show that temporal encoding with complex temporal patterns is necessary when a system must simultaneously encode signal identity (categorization) and signal intensity (regression). By analyzing the geometry of the encoding space, which describes how external inputs are mapped onto output trajectories, I clarify that multiplexing identity and intensity requires a higher-dimensional encoding space, leading to rich transient dynamics (i.e., temporal encoding). Beyond linear models, this theoretical prediction is also observed in nonlinear stochastic models and is further validated by analysis of experimental single-cell ERK activity trajectories, confirming that ERK trajectories indeed carry multiplexed information about ligand identity and dose.

Together, these results support a coherent evolutionary scenario for information-integration structures in signaling systems. Bow-tie architectures can spontaneously arise due to the physical nature of molecular interactions, and the functional demand to transmit multiplexed information (identity and intensity) through a bottleneck drives temporal encoding with complex temporal patterns. This mechanism provides a plausible design principle for the extant signaling pathways that compress diverse inputs while preserving input-specificity via rich temporal dynamics. Overall, this dissertation provides a perspective on the design principles of biological information integration and builds a foundation for understanding how primitive environmental perception emerges.