Rules for scaffold assembly in signaling

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***Short Abstract* — Effective signaling is central to cellular survival. Signaling cascades in eukaryotes often involve scaffold proteins as molecular organizers. While some scaffolds exhibit well-characterized functions, a complete theoretical understanding of the role of scaffold proteins in signaling is currently lacking. In this work, we used rule-based methods to systematically investigate model cascades with and without scaffold-based assembly mechanisms. Our findings indicate that the manner in which these complexes assemble can influence a variety of phenotypically-important network properties, including signaling speed, crosstalk, sensitivity and noise. Our findings reveal that the rules governing scaffold assembly can have a dramatic impact on network function.**

***Keywords* — Signaling Networks, Scaffold Proteins**

I. Introduction

SIGNALING networks are essential for cellular adaptation to environmental changes. Scaffold proteins are a key component of many signaling networks, since they recruit and organize other signaling proteins (*e.g.* kinases). Certain scaffolds have been extensively characterized; the prototypical scaffold Ste5 in the yeast pheromone MAP kinase cascade has been experimentally shown to take on a number of roles, including allosteric control of kinase activation (*1*). A large number of hypotheses have been put forward regarding other possible scaffold functions, including the linearization of dose-response behavior and the mediation of feedback (*2*). Despite intense investigation, however, we lack a complete understanding of how scaffolds might influence signal transduction. The goal of this work is to systematically determine how various properties of signaling cascades are impacted in the presence or absence of scaffold proteins.

To do this, we employed rule-based modeling to generate several alternative scaffold assembly scenarios and compare the dynamics of these systems with traditional kinase cascades. This allowed us to investigate what advantages might lead to the evolution of various scaffold architectures in signaling networks.

II. Results

We constructed three basic models of signaling based loosely on the network structure of the yeast pheromone signaling cascade, where an initial signal induces a phosphorylation cascade involving N kinases such that the phosphorylated N^{th} kinase is considered the output of the cascade. The control case was a *solution* model that lacked a scaffold; this kinase cascade involves a series of Goldbeter-Koshland loops (*3*) where each activated substrate is the kinase for a subsequent substrate. The *machine* model contains a scaffold that acts as a nucleation point for the hierarchical assembly of a specific multi-subunit protein complex that phosphorylates the N^{th} kinase (*4*). The *ensemble* model also contains a scaffold, however instead of an orderly assembly process, the kinases bind the scaffold independently; an ensemble-like network with numerous kinases will therefore exhibit considerable combinatorial complexity (*4, 5*).

We performed a comparative analysis of these three paradigms for cascades of varying lengths N, and found significant differences between these scenarios. For instance, only machine-like models are capable of preventing crosstalk in instances where two pathways share certain kinases. Machine-like models also exhibited far less noise than the alternative signaling paradigms as the cascades became longer. However, the assembly of the signaling machine leads to a delay in signal activation: the average first passage time for ensemble and solution signaling is significantly shorter than that for machine signaling. We also found that a machine-like cascade generally offers greater functional robustness, at the cost of evolutionary plasticity (*4*).

III. Conclusion

To systematically investigate the role of kinase scaffolding in signaling networks, we developed concise formal models of multiple possible signaling paradigms. We found that each signaling paradigm produces unique dose-dependence, dynamics, robustness and plasticity. The evolution of scaffold proteins, and the rules that govern the assembly of signaling complexes, has likely been driven by the distinct functional roles that scaffold-based signaling complexes can play.

References

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