Ensemble signaling in MAPK cascades

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***Short Abstract* — Cellular adaptation and survival depends on effective signaling mechanisms. The traditional view of signaling involves stable molecular machines that transmit information (*1*). However, the inherent combinatorial complexity of signaling networks has led to an alternative perspective in which signaling occurs via heterogeneous, *pleiomorphic ensembles* of complexes (*2*). We constructed a rule-based model of the yeast pheromone signaling network that accurately reproduces experimental data. Signaling in this model clearly occurs via ensembles of complexes, rather than reproducible signaling machines. Our results indicate that, not only is reliable signaling through pleiomorphic ensembles possible, such ensembles may promote functional plasticity in network evolution.**

***Keywords* — Signaling Networks, Pleiomorphic Ensembles**

I. Introduction

SIGNALING networks are central to a cell's ability to respond adaptively to environmental changes. Despite this, there is currently no broad consensus regarding the fundamental nature of the protein complexes such networks form. In many cases, these complexes are viewed as stable "macromolecular machines," much like the ribosome or the proteasome (*1*). Signaling networks, however, display inherent *combinatorial complexity*: that is, they can generate massive numbers of possible complexes. This fact has led to the opposing hypothesis that signaling proceeds via heterogeneous *pleiomorphic ensembles* (*2*). While this proposal is intriguing, there is currently no computational or experimental evidence to indicate that such ensembles can produce reasonable responses to signaling stimuli.

In this work, we employ rule- and agent-based modeling techniques (*3*) to study pheromone signaling in yeast. This framework allows us to consider the dynamics of the network without *a priori* reducing the number of possible species that can be generated (*4*).

II. Results

We constructed a rule-based model of pheromone signaling in yeast based on the extensive experimental characterization of the interactions in this pathway. The model itself consists of 26 types of protein agents and 253 rules governing their interactions. Each rule in this case has a rate constant associated with it; the majority of these rates have not been determined experimentally. We varied 27 of these parameters in order to obtain a set of rates that replicated experimental observations for both dose-response behavior and the dynamics of various interactions in the network. The behavior of our model is also consistent with models that utilized ordinary differential equations (*4*).

The yeast pheromone signaling network can generate around 7 million unique molecular species (*3*). As a consequence, we found that this model does not employ a small, uniform subset of complexes to respond to a signal: there is no evidence of a stable scaffold complex or any machine-like entity in our simulations. Indeed, attempts to cluster or otherwise classify the signaling complexes revealed no consistent "core complexes" either within individual simulations or between independent simulations. The observation of ensemble signaling was robust to random variations in the model's parameter set. This conserved heterogeneity suggests that ensembles may be a general property of interaction networks (*2*, *5*).

Our model exhibited relatively little noise; fluctuations in the response variables were essentially identical to the noise present in the experimental data. Thus, despite their diversity, ensembles can generate reliable responses to signal across a population of cells.

III. Conclusion

Our work indicates that pleiomorphic ensembles represent a plausible picture of signaling that is consistent with experimental measurements of the yeast MAPK network. Since ensembles can achieve reliable responses to environmental cues, it is unclear what evolutionary pressures might drive the emergence of the hierarchical assembly processes required for formation of signaling machines. Additionally, the inherent heterogeneity of ensembles may enable a degree of plasticity in network function and evolution that machines could not achieve (*6*).

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