Combinatorial Sensing in *E. coli*

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***Short Abstract* — Bacteria have a relatively small number of sensors for external stimuli, yet they are able to respond to many different environments. One mechanism that might explain this paradox is known as combinatorial sensing. We are testing whether *E. coli* uses its two component systems in order to sense in this manner and propose that signal integration occurs at the promoter level. Demonstrating that promoters can recognize patterns of sensor activity would guide future efforts to design biosensors capable of recognizing specific environments of therapeutic and practical interest.**

I. Purpose

A well-characterized example of combinatorial sensing is found in the mammalian olfactory system. In this case, a seemingly limitless number of odorants impinges on a family of receptor molecules in the nose whose specific patterns of activation are communicated to the brain where they are interpreted as smell. This and other examples of combinatorial sensing illustrate two notable advantages of such an organizing principle.[1,2] First, the broad ligand specificity of a small number of receptors allows them to respond to a large number of inputs. Second, the system can evolve to respond to new inputs without the addition of new receptors through rewiring of the system's downstream components. Thus, two minimal requirements necessary for combinatorial sensing to take place are the presence of general sensors capable of being activated to varying degrees (as opposed to all-or-none) by different stimuli and a means by which such sensor activation patterns are specifically recognized.

The idea that E. coli uses such a strategy to recognize and respond to its environment seems particularly appealing given that a few examples of general sensors capable of regulating overlapping sets of genes in *E. coli* have been reported. However, the emerging picture remains incomplete as there hasn't been a systematic study of an *E. coli* genetic network aimed at dissecting the integration of sensory inputs at the promoter level.

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II. Technical Approach

A. Determine the patterns of activation of E. coil's sensors upon exposure to a library of chemicals.

We are monitoring the activity of individual two-component systems involved in responding to stress using input-specific reporters comprising a synthetic promoter element (designed to respond to a single input) driving the expression of green fluorescent protein (GFP). Upon addition of various external stimuli we measure sensor activity by flow cytometry using such promoter GFP proxies. These data will be submitted to principle component analysis (PCA) to determine how well the sensors divide chemical space.

B. Evaluate the ability of promoters regulated by the sensors to recognize specific regions of chemical space and determine the spectrum of computations carried out at the promoter level in the E. coli stress response transcriptional network.

The activity of endogenous promoters regulated by stress sensors will be measured in cells exposed to external stimuli. We will determine the dynamic responses of the promoters as well as how the promoter responses cluster. This will reveal how specific a particular promoter is to a given stress and whether its behavior can be physiologically rationalized. Notably, this approach will also allow us to make functional predictions for less well understood output components of the network. Finally, our ability to monitor both inputs and outputs of the stress response transcriptional network will reveal the flow of information through the network and allow us to study the mechanisms of signal integration at the promoter level.

III. Conclusion

Showing that *E. coli* is capable of combinatorial sensing will provide a better understanding of the way in which bacteria sense their environment. At the same time, the potential for promoters to respond to specific patterns in sensor activity would initiate a new strategy in the design of certain types of biosensors.

References

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