Biological Constraints on Signal Integration in Bacteria

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***Short Abstract* — Cells constantly sense their environments and adjust their behavior accordingly. Bacteria often integrate information from multiple environmental inputs to modulate their gene expression states. In this work, we develop a mathematical description of signal integration based on Information Theory. Using this formalism, we explore the ability of bacteria to integrate and disentangle multiple signals using phosphorelays and show that biological signaling architectures places strong constraints on how much bacteria can learn about their external environments. As an application, we discuss information processing in the quorum-sensing circuit in the bacterium *Vibrio harveyi* where multiple signals are channeled through a common signaling circuit.**

***Keywords* — Signal Processing, Information Theory, Phosphorelays, Biomolecular Networks, Quorum Sensing.**

BACTERIA live in complex and dynamic environments. They sense and respond to both external environmental cues such as nutritional deprivation and to each other through the process of quorum sensing [1]. Adapting to changing environments often requires that bacteria integrate information from multiple environmental inputs when determining gene expression. Signal integration in bacteria occurs primarily through two-component and phosphorelay signal transduction systems [2]. Two-component systems consist of a sensor-kinase protein and a cognate response regulator. In response to an external signal, the histidine kinase transfers a phosphoryl group to the response regulator allowing it to carry out its regulatory function, usually regulation of downstream gene expression. Phosphorelays differ from two-component systems in that they often have additional regulators that allow them to integrate multiple signals. For example, in the quorum sensing circuit of the marine organism *Vibrio harveyi*, information from multiple quorum sensing molecules (autoinducers) is integrated and transduced through a single phosphorelay that regulates the expression of downstream genes [3].

To quantitatively characterize signal integration, we develop a new mathematical framework for describing signal integration in phosophorelays based on Information Theory [4]. Information theory is used extensively in engineering and neuroscience and has been recently adapted to describe gene-regulation networks with a single input and a single output [5-6]. We extend this formalism to treat signaling networks with multiple inputs and show that many standard information theoretic results from network information theory about multiple access channels are not applicable to the case at hand because biological systems are limited to "amplitude encoding".

Our formalism allows us to investigate how network architecture and kinetic parameters affect the ability of bacteria to integrate and disentangle multiple signals. We show that the ability to distinguish multiple signals using phosphorelays is strongly dependent on kinase and phosphotase rates as well as the strengths of the downstream promoters regulated by the phosphorelay. We also find that receptor clustering greatly enhances the ability for bacteria to disentangle information about multiple signals channeled through a common phosphorelay. As an application, we discuss information processing in the *V. harveyi* quorum sensing circuit.

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