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Title

Conservation of Modules but not Phenotype in Bacterial Response to Environmental Stress

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INTRODUCTION

Microbes live in changing environments and change their phenotype via gene regulation in response. Although this transcriptional response is important for fitness, very little is known about how it evolves in microbes. We started by asking a number of high-level questions about the evolution of transcriptional phenotype:

- o To what extent is transcriptional response conserved, i.e. do conserved genes respond similarly to the same condition?
- o To what extent are transcriptional modules conserved?
- o Does there exist a general stress response to a variety of stressors?

To illuminate these questions, we analyzed more than 500 microarray experiments across the bacterial domain. We looked for conservation of transcriptional regulation both in close sister species and vastly divergent clades. In addition, we produced and analyzed an extensive in-house compendium of environmental stress data in three metal-reducing bacteria.

Is phenotype conserved?

When the environment changes, do orthologous genes respond in the same way?

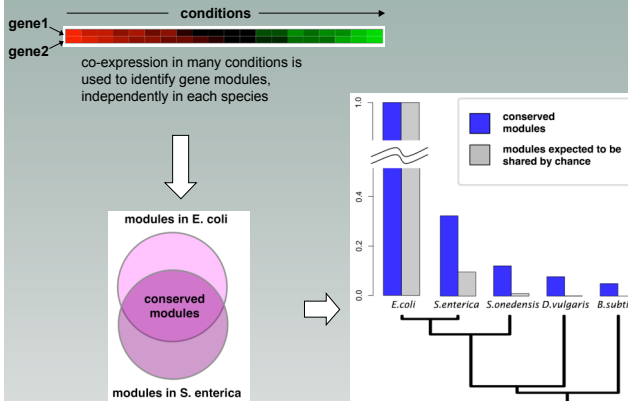
Experimental Design:

- o We studied two dissimilatory metal-reducing proteobacteria, *Shewanella oneidensis* and *Desulfovibrio vulgaris*, which are being extensively characterized for potential bioremediation applications.
- o We selected environmental stresses relevant to these organisms
- o Stressors were calibrated to have a impact on growth rate (LD50).
- o Microarray measurements before and after treatment are compared to calculate fold-change (repression or induction) of all genes.
- o We compared the response of 832 orthologous genes (BBH method)

Are gene modules conserved across bacteria?

The transcriptional network is "modular"... are these modules cohesive units in evolution?

Some co-expressed gene pairs ("modules") have been shown to be conserved from *E. coli* to yeast and metazoans. In order to assess to what extent these modules are conserved in bacteria, we collected hundreds of microarray experiments from public databases, and in each of five species to define gene modules as in (1).

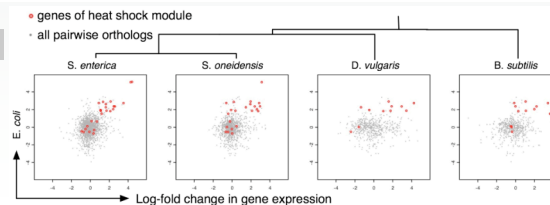


Pairs co-expressed in more than one species are conserved. For more distant species, we required modules to be conserved in the majority of intervening species.

We observe conservation at least as strong as that of protein-pairs known to physically interact. Thus, **gene modules are conserved but this does not necessarily entail conserved phenotype.**

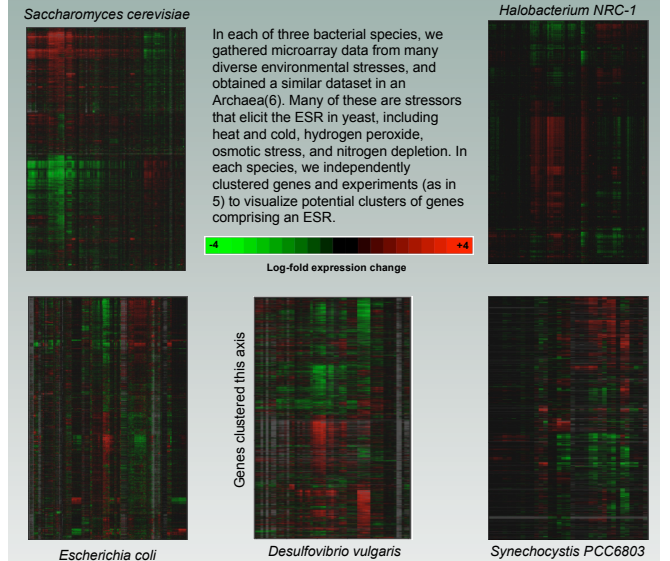
Modules' response may be conserved.

Five species' heat shock responses are compared below. While the response of all orthologous genes is uncorrelated, heat-shock annotated proteins have a more conserved response. This suggests that a core part of the response is under stabilizing selection. What about the divergence of the rest of the response? Whether it is functionally important or neutral is an important open question.



Do prokaryotes have an Environmental Stress Response ?

In many yeast species, a wide variety of environmental stresses elicits a very similar transcriptional response(5), wherein ~1000 genes are significantly induced or repressed in a nearly identical pattern. A similar type of stereotypical response has also been reported in *Plasmodium*(2). While some articles have suggested that bacteria also exhibit an ESR, we have not seen the case made as it was in yeast.



The apparent lack of ESR in three distantly related species of bacteria (a gamma-proteobacteria, delta-proteobacteria and cyanobacterium) suggests that bacteria lack an ESR that many Eukaryotes and (possibly) Archaea exhibit. This could reflect fundamental differences in the transcriptional machinery and regulatory networks of prokaryotes and eukaryotes and their response to environmental perturbation.

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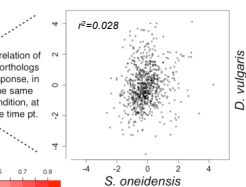
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Results:

Phenotype is not conserved. While comparisons of some time points showed modest but significant correlation, it was equally likely to be positive as negative, and the similar part of the response to consist of a few operons. We also found no conservation of response to salt or nitrate stress in two obligate anaerobic delta-proteobacteria (*G. metallireducens* and *D. vulgaris*).

We searched public databases to interrogate a wider breadth of stress conditions with data in closely related species, and in no case did we find conservation, even in the response of close sister species *S. enterica* and *E. coli* to heat stress.



scatter plots legend

