"Evolution of Bacterial Regulatory Networks: the role of DNA-binding specificity"

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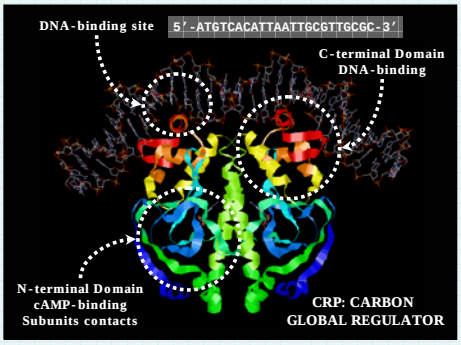
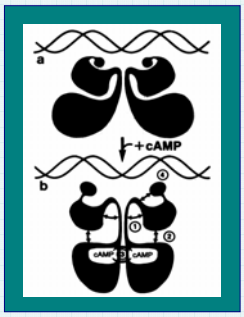
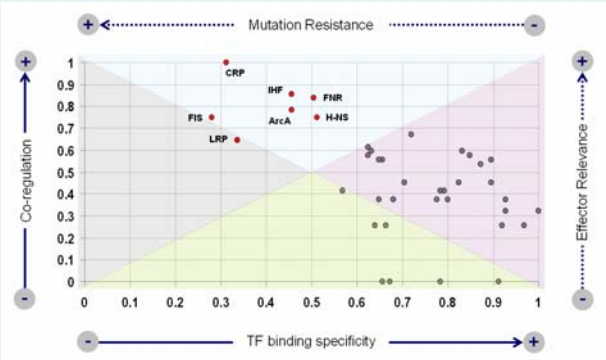
A conceptual model for the evolution of Transcriptional Regulatory Networks





ROLE OF EFFECTOR: CRP-AMPc. Garges & Adhya *Journal of Bacteriology Vol.170 No.4 pp.1417-1422, 1988*



This plot shows variables that affect the evolution of protein regulators and their target genes. The subplot (a) represents the components of *DNA-binding specificity* in the Regulator (TF): the DNA-binding domain and the DNA site. The subplot (b) shows a theoretical variable that is not easily measured, *effector relevance*, that we anticipate can play an important role here. In the subplot (c) summarizes the main observations of this work; two main variables are considered: *binding specificity* and frequency of *co-regulation*, normalized in a [0-1] scale. Note that a scatter plot of these two variables clearly separates *global transcription factors* (plotted in red) from the other regulatory proteins, highlighting their potential diagnostic value. The model proposes to use the degree of co-regulation as an indirect measure of effector relevance, similarly to *mutation resistance*, which is represented as being inversely proportional to DNA-binding specificity.

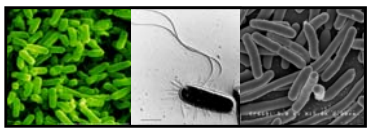
INTRODUCTION

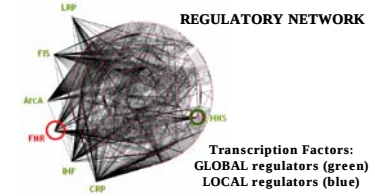
Evolution is the result of the variation and selection through time of the components and structure of the organisms. ***Transcriptional regulation*** plays a prominent role in the evolution of living variation because it controls the cellular response to environmental changes through activity of regulatory proteins (***Transcription Factors***, TFs) and the expression levels of their target genes.

Understanding the mechanisms by which gene regulatory networks change through evolution is a fundamental problem. Here we assess a part of this question analyzing the molecular property of *DNA-binding specificity* of two types of gene regulators from *Escherichia coli* and *Bacillus subtilis*: the *global TFs* (regulator of several genes) and *local TFs* (regulator of few genes).

DNA-binding specificity is defined as the ability of DNA-binding proteins (i.e. TFs) to discriminate a small subset of DNA sequences from the vast repertoire of sequences found in a genome. In this work, we tried three different measures of this property and we obtained compatible results with all of them. (We only show here the measure based on the diversity of DNA binding sites - Information Content). We conclude that *DNA-binding specificity* is a predictor of the role of TFs in the regulatory networks of living systems.

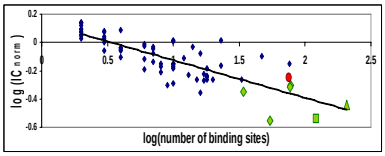
Escherichia coli



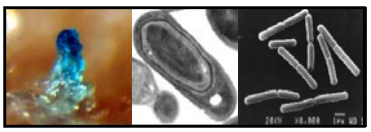


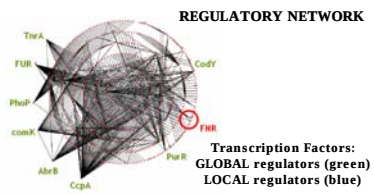
REGULATORY NETWORK

Transcription Factors:
GLOBAL regulators (green)
LOCAL regulators (blue)



Bacillus subtilis





REGULATORY NETWORK

Transcription Factors:
GLOBAL regulators (green)
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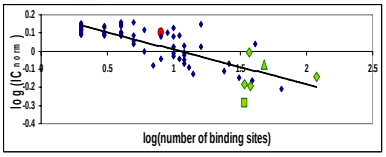


METHODOLOGY AND RESULTS

Figure 2. Low specificity transcription factors show high expression levels

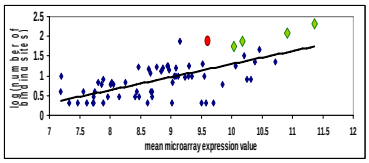
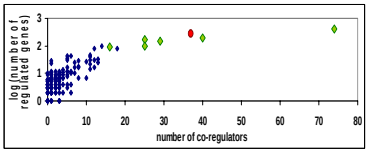
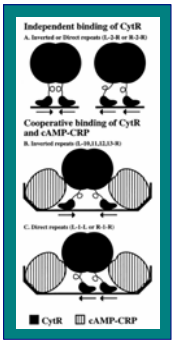


Figure 3. Adding co-regulation to binding specificity





CO-REGULATION OF CytR-CRP. Pedersen & Valentin-Hansen *The EMBO Journal Vol.16 No.8 pp.2108-2118, 1997*

We have also found that low specificity regulators (dots in green and Oxygen regulator in red) are transcribed at relative high levels in *E. coli* (see Figure 2), perhaps as a consequence of these proteins not being co-localized with their target genes in the genome, suggesting that an efficient occupancy of DNA binding sites may be achieved by high copy number instead.

In addition, it is clear from Figure 3 that less specific regulators have more co-regulators, other TFs that help translate their global control to more specialized subsets of target genes (see an example in the Figure to the right), adding one more variable to this evolutionary scenario.

Figure 1. Diversity of DNA binding sites as a measure of binding specificity

Information Content (DNA binding sites) from Oxygen regulator (FNR)

Figure 1 provide a picture of bacterial regulatory networks in which binding specificity is a predictor of the hierarchy of any Transcription Factor (TF/regulator). Global TF regulators (dots in green) from two bacterial models with remarkably different life styles and long phylogenetic distance consistently display low binding specificities, and that specificity values of most orthologous TFs between *E. coli* and *B. subtilis* (Oxygen regulator in red) are congruent with their global or local (metabolic/ecological) role in these species.

Our data suggest that the ability of regulators to conserve or gain new target genes in each organism is at least correlated to their power to discriminate DNA sequences near to genes in the genome.