THE FUNCTIONAL ARCHITECTURE OF *ESCHERICHIA COLI* IS REVEALED BY A NATURAL DECOMPOSITION APPROACH

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For more than 20 years it has been recognized that transcriptional regulatory networks (TRNs) comprise complex circuits with different control levels. Indeed, evidence suggests that TRNs show a hierarchical organization of modularity. Previous studies have used different methods in an effort to extract the modular organization of transcriptional regulatory networks. However, these approaches are not natural, as they try to cluster strongly connected genes into a module or locate known pleiotropic transcription factors in lower hierarchical layers. In this work, we nravel the TRN of *Escherichia coli* by separating it into its key elements, thus revealing its natural organization. Contrary to previous reports, we found that the TRN is not acyclic; rather it exhibits feedback loops bridging different hierarchical layers. Based on the topological features, we propose a mathematical criterion to classify the network elements into one of two possible classes: hierarchical or modular genes. We found that modular genes are clustered into physiological correlated groups or modules. On the other hand, we observed that hierarchical elements highly correlate with the known global transcription factors (TFs), suggesting that this could be the first mathematical criterion to identify global TFs in a cell. Furthermore, we identified a new element in TRNs: intermodular genes. These are structural genes which integrate, at the promoter level, signals coming from different modules, and therefore from different physiological responses. Then, using the concept of pleiotropy, we reconstructed the hierarchy governing the TRN, taking into account the presence of feedforward motifs and feedback loops bridging different organizational levels. Finally, we analyzed the role that feedforward motifs play shaping the hierarchical backbone of the TRN. This study sheds new light on the design principles underpinning the organization of TRNs, showing a novel nonpyramidal architecture comprising independent modules globally governed by hierarchical TFs, whose responses are integrated by intermodular genes.

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