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## Model-Driven Elucidation of Nitrogen Transcriptional Regulatory Network in Bacteria

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A model-driven approach to experimental design was applied to elucidate the transcriptional regulation by two major transcription factors, NtrC and Nac, in nitrogen metabolism of *Escherichia coli*. Genome-wide measurements with ChIP-exo and RNA-seq were performed using alternative nitrogen sources predicted by genome-scale models to activate these responses and to make differential activation of Nac. A total of 19, 249, 153, and 2171 binding sites for NtrC, Nac, RpoN and RpoD, respectively were identified, and NtrC associates preferentially with RpoN-dependent promoters, while Nac interacts with RpoD-dependent promoters. Functional analysis of the two regulons showed that the NtrC regulon primarily responds to nitrogen limitation by attempting to increase nitrogen availability. Nac, on the other hand, re-balances flux through carbon metabolism to accommodate the change in the nitrogen source. A systems-biology computational approach was required to reconcile the behavior of these two transcription factors into a detailed and quantitative understanding of how the metabolic network responds to different nitrogen sources.