

How gene order is influenced by the biophysics of transcription regulation

What are the forces that shape the structure of prokaryotic genomes: the order of genes, their proximity, and their orientation? Coregulation and coordinated horizontal gene transfer are believed to promote the proximity of functionally related genes and the formation of operons. However, forces that influence the structure of the genome beyond the level of a single operon remain unknown. Here, we show that the biophysical mechanism by which regulatory proteins search for their sites on DNA can impose constraints on genome structure. Using simulations, we demonstrate that rapid and reliable gene regulation requires that the transcription factor (TF) gene be close to the site on DNA the TF has to bind, thus promoting the colocalization of TF genes and their targets on the genome. We use parameters that have been measured in recent experiments to estimate the relevant length and times scales of this process and demonstrate that the search for a cognate site may be prohibitively slow if a TF has a low copy number and is not colocalized. We also analyze TFs and their sites in a number of bacterial genomes, confirm that they are colocalized significantly more often than expected, and show that this observation cannot be attributed to the pressure for coregulation or formation of selfish gene clusters, thus supporting the role of the biophysical constraint in shaping the structure of prokaryotic genomes. Our results demonstrate how spatial organization can influence timing and noise in gene expression.

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