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Intrinsic limits to gene regulation by global crosstalk¹ TAMAR FRIEDLANDER, ROSHAN PRIZAK, CALIN GUET, NICHOLAS H. BARTON, GASPER TKACIK, Institute of Science and Technology Austria — Gene activity is mediated by the specificity of binding interactions between special proteins, called transcription factors, and short regulatory sequences on the DNA, where different protein species preferentially bind different DNA targets. Limited interaction specificity may lead to crosstalk: a regulatory state in which a gene is either incorrectly activated due to spurious interactions or remains erroneously inactive. Since each protein can potentially interact with numerous DNA targets, crosstalk is inherently a global problem, yet has previously not been studied as such. We construct a theoretical framework to analyze the effects of global crosstalk on gene regulation, using statistical mechanics. We find that crosstalk in regulatory interactions puts fundamental limits on the reliability of gene regulation that are not easily mitigated by tuning proteins concentrations or by complex regulatory schemes proposed in the literature. Our results suggest that crosstalk imposes a previously unexplored global constraint on the functioning and evolution of regulatory networks, which is qualitatively distinct from the known constraints that act at the level of individual gene regulatory elements.

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