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SHORT TANDEM REPEATS RECRUIT TRANSCRIPTION FACTORS TO TUNE EUKARYOTIC GENE EXPRESSION

Transcription factors (TFs) regulate gene expression via sequence-specific binding to regulatory elements in genomic DNA. Short tandem repeats (STRs) are enriched in these regulatory elements and have been widely associated with changes in gene expression, but the mechanism by which STRs modulate expression remains unknown. To address this gap, we leveraged the MITOMI microfluidic platform to measure equilibrium binding and kinetics of basic-helix-loop-helix TFs Pho4 and MAX to their consensus binding sites, surrounded by various random or repetitive sequences. In total, we report >6800 equilibrium constants (K_d's) for >600 protein-DNA sequence pairs and >2100 dissociation rate constants (k_{off}'s) for >60 protein-DNA sequence pairs for WT and mutant variants of MAX and Pho4. Our measurements reveal that STRs can modulate affinities by >2 kcal/mol, equal to a ~30-fold change in binding, despite no predicted effect of STRs from current binding models. Via direct measurements and statistical mechanical modeling, we establish that STRs modulate equilibrium occupancy by binding TFs directly through a combination of enthalpic and entropic factors: repetitive sequences represent low-affinity binding sites within a rugged energy landscape arranged with a particularly high multiplicity. By combining measured dissociation rate constants with continuous-time Markov chain modeling, we further establish that STRs can accelerate *in vivo* target searches. Neural network models of Pho4 and MAX binding trained only on *in vivo* genome-wide occupancies (*e.g.* ChIP-nexus) correlate with the direction and magnitude of *in vitro* TF-STR binding, suggesting that STRs provide an easily evolvable mechanism by which gene expression can be tuned in cells. Finally, we provide evidence that >80% of TFs previously characterized *in vitro* show significant binding to STRs, and we validate the accuracy of these predictions via direct measurement of Nrg1 (a zinc finger TF) binding to various STRs.

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