

Of *cis*, *trans* and feedback regulation: Dissecting local regulation in yeast

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Abstract. The vast majority of regulatory genetic variants are found in close vicinity of the regulated gene. The distinction between *cis*- and *trans*-acting variants is a fundamental starting point to understand the mechanisms underlying these regulatory variants. Typical *cis*-regulatory variants affect transcription factor binding sites or RNA stability. Local *trans*-regulations have been less studied and include feedbacks, an essential regulatory feature of biological systems. To understand the contribution of *cis* and *trans* regulation and their potential interplay, we devised a novel experimental design in which allele-specific expression in a hybrid cross of two yeast strains is compared to allele-specific expression in a pool of segregants of the same cross. We implemented a statistical procedure based on generalized linear models for RNA-seq count data to quantify the contribution of *cis* and *trans* effect in local regulation. Our model allows controlling for allele selection in the pool population by integrating robust estimates of allele frequency from genomic DNA sequencing. Applied to a cross of two distant yeast strains, our analysis revealed significant differences of *cis*-effects among major gene categories (essential, non-essential, and non-coding). Furthermore, our results shed light on the effects of feedback in buffering or enhancing the impact of genetic variation on gene expression.