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Origins of extrinsic variability in eukaryotic gene expression DMITRI VOLFSON, JENNIFER MARCINIAK, UC San Diego, WILLIAM J. BLAKE, Boston University, NATALIE OSTROFF, LEV S. TSIMRING, JEFF HASTY, UC San Diego — Variable gene expression within a clonal population of cells has been implicated in a number of important processes including mutation and evolution, determination of cell fates and the development of genetic disease. Recent studies have demonstrated that a significant component of expression variability arises from extrinsic factors thought to influence multiple genes in concert, yet the biological origins of this extrinsic variability have received little attention. Here we combine computational modeling with fluorescence data generated from multiple promoter-gene inserts in *Saccharomyces cerevisiae* to identify two major sources of extrinsic variability. One unavoidable source arising from the coupling of gene expression with population dynamics leads to a ubiquitous noise floor in expression variability. A second source which is modeled as originating from a common upstream transcription factor exemplifies how regulatory networks can convert noise in upstream regulator expression into extrinsic noise at the output of a target gene. Our results highlight the importance of the interplay of gene regulatory networks with population heterogeneity for understanding the origins of cellular diversity.

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