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A single-molecule view of gene regulation in cancer

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Single-cell analysis has revealed that transcription is dynamic and stochastic, but tools are lacking that can determine the mechanism operating at a single gene. Here we utilize single-molecule observations of RNA in fixed and living cells to develop a single-cell model of steroid-receptor mediated gene activation. Steroid receptors coordinate a diverse range of responses in higher eukaryotes and are involved in a wide range of human diseases, including cancer. Steroid receptor response elements are present throughout the human genome and modulate chromatin remodeling and transcription in both a local and long-range fashion. As such, steroid receptor-mediated transcription is a paradigm of genetic control in the metazoan nucleus. Moreover, the ligand-dependent nature of these transcription factors makes them appealing targets for therapeutic intervention, necessitating a quantitative understanding of how receptors control output from target genes. We determine that steroids drive mRNA synthesis by frequency modulation of transcription. This digital behavior in single cells gives rise to the well-known analog dose response across the population. To test this model, we developed a light-activation technology to turn on a single gene and follow dynamic synthesis of RNA from the activated locus. The response delay is a measure of time required for chromatin remodeling at a single gene.