Gene regulation as a nonlinear noise filter

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A common knowledge is that positive feedback loop in gene regulation can give rise to bistability, resulting in a phenotypic differentiation of a population of genetically identical cells. But what happens if a positively self-regulated transcription factor initiates the activity of other genes? If gene expression were a deterministic process, then bistability at the level of transcription factors would propagate downstream to the proteins that they regulate. Gene expression is, however, an inherently stochastic process. At each level of gene regulation, be it self-regulation of regulatory gene, or regulation of target gene by the upstream regulator, the fluctuations in protein concentrations are filtered in a nonlinear manner, which distorts their probability distributions. As a result, the mapping between the shapes of the transcription factor distribution and target protein distribution is no longer as simple as unimodal to unimodal, and bimodal to bimodal. Instead, it depends on the overlap, or lack thereof, between the sensitivity regions of dose-response curves of each promoter. We show that, in this way, a single regulator can induce qualitatively different responses of different targets to increasing levels of an external signal: Some responses can be graded (unimodal distribution with varying position of its peak), and some others can be binary (unimodal-bimodal-unimodal transition). The problem of differential interpretation of the same input by different target genes is an emerging field in quantitative biology. It has been known to date that more and less sensitive promoters respond sequentially to increasing signal, as this is intuitively obvious from the comparison of dose-response curves of different promoters. However, the shapes of these responses (binary or graded) and their interdependence have been rarely investigated in systematic experimental studies, especially in the case of multiple targets of a single regulator. Our study demonstrates a possible mechanism based on both stochasticity and nonlinearity of biochemical reactions, due to which different genes can interpret the same biological signal in a different way.

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[2] A. Ochab-Marcinek, M. Tabaka, PNAS **107(51)**, 22096 (2010).

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