Error correction strategies of cells: Team proposes new hypothesis

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Cells dynamically respond to environmental signals by turning appropriate sets of genes on or off. The "control system" that determines which genes need to be expressed at what time depends primarily on the interactions between transcription factor proteins (TFs) and the regulatory DNA sequence. This system is highly complex—especially in cells of multicellular organisms—as correct combinations of TF molecules need to bind specific sites on the DNA. Surprisingly, while multicellular organisms need to regulate more genes compared to bacterial cells, their TFs are less specific and bind promiscuously on many genomic locations, including unsuitable ones. So how can TFs reliably turn on the correct gene, while avoiding erroneously turning on the others?

Models of gene regulation proposed to date rest on the assumption of a "thermodynamic equilibrium," in which the interactions between TFs and DNA take on a simple theoretical form. These models seem to concur with the results of experiments with bacterial cells. However, they do not consider the fact that the seemingly low specificity of TFs for their regulatory sites in multicellular organisms could induce erroneous expression of genetic information. This would lead to unwanted interactions, the so-called crosstalk, with disastrous consequences for the cell.

Gasper Tkačik, Assistant Professor at IST Austria, together with graduate students Sarah Cepeda-Humerez and Georg Rieckh, examine this scenario in their paper published on December 4, 2015, in the

Physical Review Letters. They investigate the importance of crosstalk and its effects, and propose an alternative model that suppresses erroneous initiation. Their work extends the concept of kinetic proofreading, which was proposed in the 70's to explain how certain enzymes can react only with correct substrates amongst a large excess of similarly-looking, but incorrect, substrates. This mechanism has also been crucial in understanding the fantastic ability of the cells to replicate their DNA prior to cell division with extremely high fidelity. Proofreading, as applied to gene regulation, leads to more accurate results and also works in cases of low concentration of TFs. However, it also comes with a price tag, as the cell needs to invest more energy but also more time to accomplish the task of regulating its gene expression.

This tradeoff between speed and specificity in proofreading has been examined before. What is novel in the recently published paper, however, is the stochastic formulation of kinetic proofreading explored by Tkačik and colleagues: here, while proofreading reactions provide increased specificity, these reactions take place amongst only a few handful of molecules, and thus lead to increased noise in gene expression. It is therefore unclear whether decreases in crosstalk due to proofreading would not be swamped by an increased noise in gene expression. The authors computed the optimal strategy for the cells to find that proofreading in gene regulation could provide a vast improvement over regulation at thermodynamic equilibrium for multicellular organisms.

While the authors cannot theoretically exclude the existence of a complex equilibrium scheme that reduces crosstalk in gene regulation for multicellular organisms sufficiently, their results suggest that equilibrium solutions, if they exist, are not simple. Their paper advances an alternative hypothesis to mitigate the crosstalk problem in the form of an out-of-equilibrium, proofreading-based transcriptional regulation. By presenting indirect evidence consistent with such a mechanism and

proposing direct experimental tests, the authors call for a critical re-evaluation of the textbook assumption of equilibrium in gene regulation.

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