Separating News from Noise

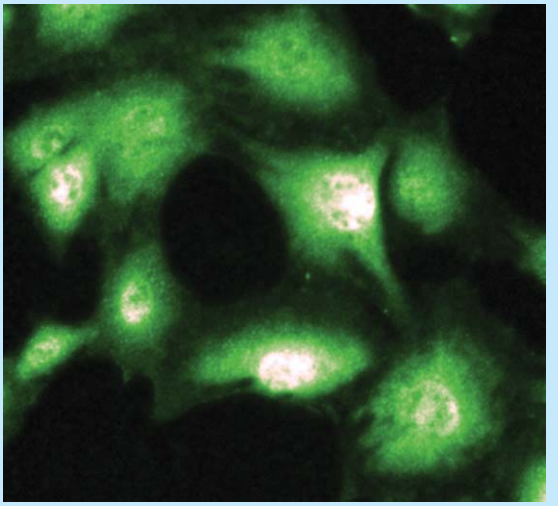
Cells attempting to interpret environmental signals face the same challenge as guests attempting conversation at a crowded party: trying to extract meaningful information against a backdrop of distracting noise. By determining the level and impact of noise within a given system, scientists might understand the extent to which a cell can selectively respond to signals of varying magnitudes.

Cheong *et al.* have tackled this problem by employing a model based on the information theory metric of 'mutual information,' wherein binary bits represent the number of ligand concentrations that a cell can discern and resolve with an appropriate output.

By treating mouse fibroblasts with varying concentrations of tumor necrosis factor (TNF) and measuring the resulting shifts in the production of transcription factors NF-κB and ATF-2, the researchers determined that individual cells are essentially capable of a one-bit response to this ligand, where signaling is simply on or 'off.' Many intermediate steps lie between TNF and NF-κB, and the authors modeled signal transmission in this pathway as a 'tree' network. In this model, information is transmitted along a single 'trunk,' in which noise can have a major impact and introduce bottlenecks in signal transmission, before branching out to yield different outputs. Endogenously-produced TNF inhibitors can dampen noise arising within this system, but also limit the ultimate dynamic range of signal response.

Ensembles of cells exhibited strikingly different 'bush' network behavior, in which signals are transmitted to different outputs along independent channels with no shared bottleneck, and a group of 14 fibroblasts proved capable of a 1.8-bit response. These data indicate that this network modeling approach could potentially reveal valuable new insights into the variable impact of biochemical noise in biological systems. – *Michael Eisenstein*

Cheong, R. *et al. Science*, Published online 15 September 2011, doi: 10.1126/science.1204553.



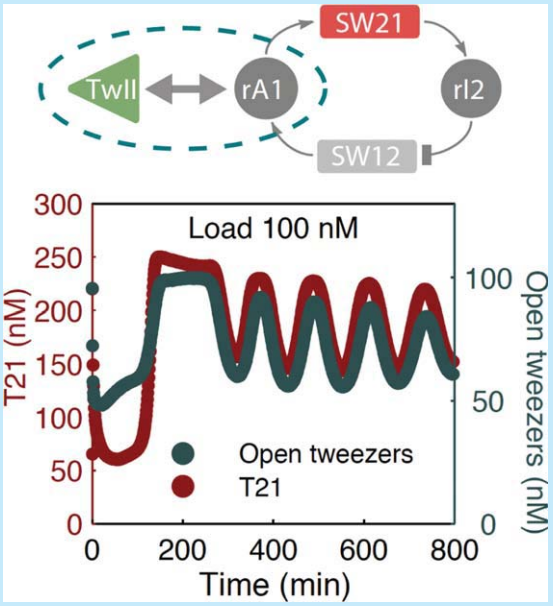
Circuits that Keep Their Rhythm

The interplay between different genes can give rise to periodic, oscillatory expression patterns, and some preliminary experiments have demonstrated the potential to design synthetic systems that recapitulate such behavior and act as molecular 'timers.'

By building on previous work with nucleic acid-based oscillators, Franco *et al.* have obtained valuable insights that might lead to improved stability for such constructs. To begin, they performed numerical simulations to examine the oscillatory behavior of a system driven by the *in vitro* transcription of two small 'genelets,' each of which produces an RNA molecule that regulates the activity of the other.

After identifying stable operating conditions, they introduced a 'load'—a molecule that generates detectable output in response to oscillator activity. The researchers noted that the core oscillator tended to be destabilized when it was coupled directly to load activation. However, the introduction of an insulator 'genelet,' which gets switched on by oscillator output RNAs and in turn produces a secondary signal that interacts with the load, enabled the system to function stably even in the presence of large and potentially disruptive load concentrations.

The investigators subsequently confirmed the predictions from their simulations in a series of experiments in



which the multi-genelet circuit was coupled to a load that consisted either of a 'DNA tweezers' molecule that generates an optical readout or a gene encoding a dye-binding aptamer. Both systems benefited substantially from the presence of an insulator, highlighting a strategy that could support future efforts to engineer robust, self-regulating biological systems. However, their experimental data also deviated from the numerical models to an extent that highlights the potentially confounding complexity inherent to even the simplest biochemical networks. – *Michael Eisenstein*

Franco, E. *et al. Proc. Natl. Acad. Sci. USA*, **108**, E784–93 (2011).

Editors with an Eye for Nonsense

Enzymes known as adenosine deaminases (ADARs) bind to double-stranded RNA (dsRNA) molecules and catalyze the conversion of adenosine nucleotides to inosine, although the purpose of this modification remains enigmatic. ADAR activity appears to be somewhat promiscuous, and it has proven difficult to authoritatively identify specific targets of A-to-I editing.

Loss of ADAR function is lethal for many organisms but results in relatively minor defects in *Caenorhabditis elegans*, and Wu *et al.* used this worm model to examine how RNA processing is affected by the absence of these enzymes. In particular, the researchers sought to follow-up on earlier findings suggesting that ADAR operates in parallel with the RNAi machinery as a competitive mechanism for dsRNA processing.

They isolated and sequenced numerous 23- and 24-nucleotide RNAs that were specifically overexpressed in *C. elegans* lacking ADAR enzymes. The majority of the transcripts could be mapped to one of 454 ADAR-modulated RNA loci (ARLs); these generally tended to be associated with annotated transposons or inverted repeats rather than transcribed genomic regions. A parallel, computational analysis of the sequencing data confirmed that transcripts subject to A-to-I editing largely tend to be associated with these ARLs.

Levels of ARL-associated RNAs could be normalized by generating ADAR knockout worms that also lacked RDE-1, an enzyme associated with RNAi processing. Indeed, the researchers observed several pieces of evidence suggesting that ADAR processing prevents dsRNAs from entering the RNAi pathway; for example, two transcribed regions associated with ARLs were specifically downregulated in ADAR knockout animals, suggesting siRNA-mediated inhibition.

These findings suggest the possibility that ADAR may act to prevent the accumulation of nonfunctional or undesirable dsRNAs that might otherwise disrupt cellular function by activating the RNAi pathway. – *Michael Eisenstein*

Wu, D. *et al. Nat. Struct. Mol. Biol.* Published online 11 September 2011, doi: 10.1038/nsmb.2129.