structure can be thought of as a long “green” tail distribution of many small savings that add up to a major opportunity for reducing energy consumption, while also improving a building’s responsiveness to its occupants. This presents corresponding challenges that are at the frontiers of distributed computing and communications; rather than replicating the history of their development, today’s best practices can be extended to this largest of all programming environments—the built environment.

References and Notes
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MOLECULAR BIOLOGY

Reliable Noise
David Levens¹ and Ashutosh Gupta¹²

Most measurements of gene expression assess large numbers of cells to improve precision and reduce the “standard error” (the standard deviation of the mean). Yet, the standard deviation of the fluctuations of a measured property, such as cell proliferation, over time in a single cell (in a system at equilibrium or steady state) or across a cell population, scaled to the mean of the measured property, is defined as “noise.” Despite this pejorative, a full accounting of noise provides insights into the pathways and mechanisms controlling a measured property. On page 1142 of this issue, To and Maheshri demonstrate that noise itself can generate a system that switches spontaneously between high and low gene expression (1). This finding implies that fluctuation in the numbers of regulatory molecules may drive physiological transitions without having to precisely specify the numbers of other molecules needed to prepare chromatin and make RNA. However, these same fluctuations might initiate and sustain pathological states, so mechanisms to suppress such fluctuations must also exist.

The basic experimental scheme used by To and Maheshri involves expressing TetVP16, a recombinant transcription factor, from a weak minimal promoter bearing either one or seven binding sites for TetVP16 itself. This positive feedback arrangement mimics a commonly occurring biological regulatory motif (2). Reporter genes encoding fluorescent proteins that are driven by either promoter are then used to monitor transcriptional output in cells. Upon the graded removal of doxycycline, a compound that inhibits the binding of TetVP16 to DNA, a cell population can transition from low to high reporter gene expression in this system.

To and Maheshri observed that with a single TetVP16 binding site in the promoter, the entire cell population increased reporter gene expression gradually and coherently. However, with seven TetVP16 binding sites, even at low doxycycline concentrations, a single burst of transcription could drive enough TetVP16 expression to enable visualization by sustained high reporter expression, the result of a high transcription output state in individual cells that sporadically relaxed to low output. The high-output state was associated with bursts of transcription that were less frequent, and either of longer duration or of higher intensity compared to bursts observed in the low-output state. Because only a single polymerase can initiate transcription at a promoter at one time, prolonging a burst to include more successive rounds of transcription initiation will increase output relative to more frequent, but short bursts.

The same bimodal pattern of low and high gene expression was also observed with a stronger promoter bearing just one TetVP16 binding site. Thus, cooperative binding of TetVP16 was excluded as the cause of the switch from low to high transcription output. This two-state system is distinct from the monotonic curve defined by calculations based solely upon the binding constants and concentrations of interacting molecular species in the absence of cooperativity. The study of To and Maheshri also reveals the difficulty of rigorously accounting for the biologically relevant species of macromolecules. To construct a working mathematical model, the authors had to correct for a cytoplasmic reservoir of inactive TetVP16 molecules and for dynamic system stability. The fraction of cells expressing a gene is a function of the concentration of an effector molecule (as in the system used by To and Maheshri). At very low or high effector concentrations, the expression system is often off (gray) or on (green). At intermediate concentrations, the system is bimodal, flipping between both states (region with lines). Nevertheless, the overall system is stable.
the ubiquitination of TetVP16, a modification that generates the most transcriptionally relevant species, but a species that is unstable (marked for proteolysis).

Cross-regulating and self-regulating transcription factor regulatory circuits are common, and describing how noise is suppressed or amplified as it is transmitted through these networks may be essential to understanding their operation. The inherent statistical fluctuations around the mean output of a weak promoter [about one transcript per cell (3)] generate intrinsic noise. For long-lived gene products, this noise can be averaged away over time. But if the gene product is a short-lived transcription factor, then this intrinsic noise is amplified and propagated onto each of the transcription factor’s target genes as extrinsic noise (4–6). Depending on the quality and number of transcription factor binding sites, as well as on the architecture, context, and strength of their associated promoters, different target genes may be tuned to switch to high output at different concentrations of transcription factor (7). Positive feedback onto the gene encoding the transcription factor itself, fixes the stochastic switch in the “on” position.

Such stochastic switching in a uniform population of unicellular organisms generates a range of responses to a defined stress and increases the likelihood of survival. This sort of switching may also be critical during metazoan development. Whereas the nematode Caenorhabditis elegans hardwires the fate of each of its 959 cells (8), the 10^{13} cells of the human body are unlikely to be explicitly programmed, and so some form of probabilistic specification is required. When the number of cells in a developmental field is sufficiently large, precise stochastic switching may be guaranteed by chance. This would seem to be especially appropriate for genes encoding effectors whose synthesis and release from a small number of cells elicit a cell nonautonomous response, ultimately recruiting a cohort of cells to the same switched fate. Thus, a defined physiological or developmental state may be viewed as an “attractor” (9), generating a stable system, despite the fluctuations of individual cells (see the figure).

However, for some genes, even a pulse of inappropriate expression may provoke untoward consequences, and so unscheduled stochastic switching may need to be suppressed in some cases. For example, even a brief increase in the concentration of the transcription factor Myc in some cells provokes programmed cell death (10). The problem becomes how to suppress stochastic pulses that might put the system into an unfavorable state, while ensuring that proper switching, driven by bona fide signaling, is allowed (11). End-product feedback regulation would be inherently too slow to control noise in this situation. Indeed, in the case of human Myc, transcription generates dynamic DNA supercoiling that when sufficiently intense, provokes a change in DNA conformation. This threshold-dependent change in DNA conformation serves as a real-time sensor of the intensity of ongoing transcription, enabling the effectors of this system to intercept incipient fluctuations and suppress noise, while transmitting true signals (12–14). Similar adaptations might be anticipated for genes that are required at uniform, low levels of expression, whereas other mechanisms are likely to expand the dynamic ranges of genes, probing the limits of expression space.

References and Notes

GEOPHYSICS

Changing Views of the San Andreas Fault

Katherine Scharer

A combination of high-resolution laser imaging with improved radiocarbon dating techniques is providing an exciting new view that questions fault behavior models that have been applied to the south central San Andreas Fault for decades, highlighting the value of revisiting old problems with new techniques.

Fault behavior models describe the amount of slip (the relative displacement of points on opposite sides of a fault), length, and location of ground-rupturing earthquakes along a fault (see the figure, panels A and B). In the 1980s, observations of 8 to 10 m of slip measured for the most recent large earthquake (in 1857) and inferred for the two preceding earthquakes along the Carrizo Plain section of the southern San Andreas Fault contributed to the development of the characteristic and uniform slip models (6, 7). A fundamental premise of both models was that every rupture that crossed a specific region of the fault produced similarly large slip, and thus controlled the frequency of earthquakes along that segment. If correct, then the timing of large ruptures like the M7.9 in 1857 seemed to be controlled by properties of the fault in the Carrizo Plain (8). In comparison, the variable-slip model allows the slip, rupture location, and length to change with each earthquake (6).

The magnitude 7.0 earthquake that struck Haiti on 12 January 2010 is a reminder of the devastation caused by large earthquakes. Because recurrence of large (M7–8) earthquakes is rare, on the order of centuries, studying the past behavior of a fault guides future expectations. Paleo-seismologists examine the stratigraphic and geomorphic history of deposits and landforms along a fault for evidence of past ruptures. Such observations provide information on when earthquakes happened, what parts of the fault failed, and the size of the earthquakes. The collected geologic data form the backbone of probabilistic seismic hazard analyses (1) used by the insurance and engineering industries and are increasingly used to explore models of lithosphere rheology and fault interaction (2, 3). Because of sparse data, however, inferences about patterns of strain accumulation and release are a common occurrence. On pages 1119 and 1117 of this issue, Ziolkiewicz et al. (4) and Grant Ludwig et al. (5) present data and interpretations providing an exciting new view that questions fault behavior models that have been applied to the south central San Andreas Fault for decades, highlighting the value of revisiting old problems with new techniques.

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PERSPECTIVES

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