GENOMICS

E. coli, What a Noisy Bug

Investigators detail striking genome-wide variation in gene expression between individual cells.

Sanjay Tyagi

To study gene expression, researchers often grind up a large number of cells grown under the same conditions and then measure the amounts of gene products, such as messenger RNAs (mRNAs) and proteins, in the soup. Many recent studies, however, have pointed out that beneath such average measurements lies great variation among individual cells, sometimes referred to as "noise" (*1*, *2*).

In multicellular organisms, studies of noise have raised questions about how tissue specificity is maintained in the face of great variation (*2*). In unicellular organisms, researchers have found that noise can give rise to groups of cells within a genetically homogenous population that behave differently (*3*). By measuring noise in the genomes of different organisms, researchers can explore its evolutionary and functional importance (*4*). On page 533 of this issue, Taniguchi *et al*. (*5*) contribute to this effort by reporting the absolute numbers of, and cell-to-cell variation in, protein molecules present in single *Escherichia coli* cells for a set of 1018 genes covering about one-fourth of the genome. They also provide simultaneous counts of mRNA molecules for a smaller set of 137 genes that are abundantly expressed.

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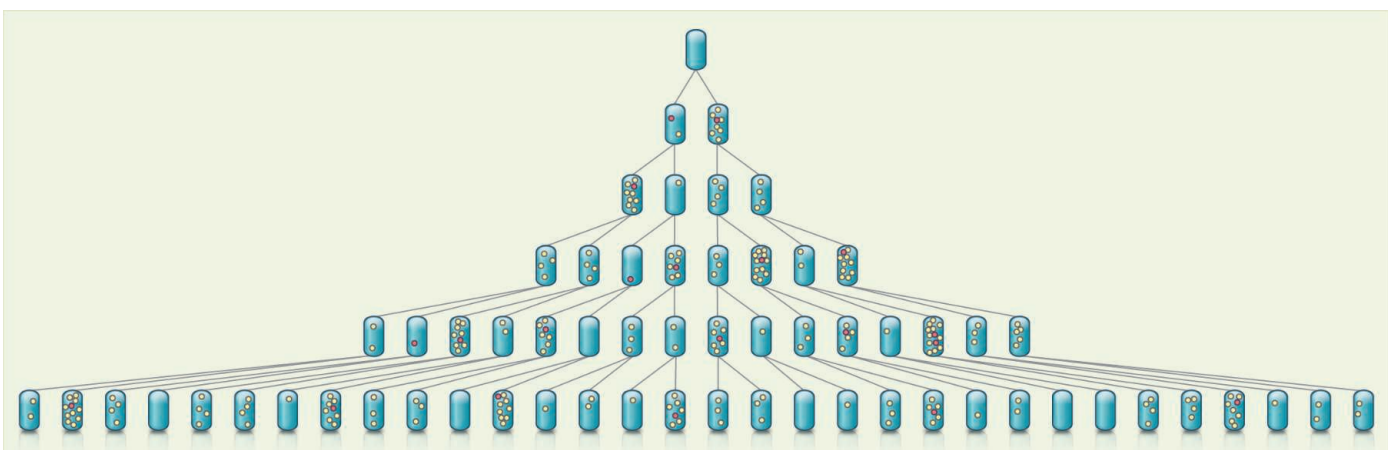
The authors used a combination of fluorescence microscopy and a library of genes tagged with fluorescent labels in a system automated for high through-put to count molecules in individual cells. They found that, depending on the gene, each cell contained 0.1 to 10,000 copies of each protein and 0.05 to 5 copies of each mRNA species. The ratio of mRNA to protein ranged from 1:100 to 1:10,000. At a given moment, a fraction of *E. coli* cells will not have even a single molecule of certain proteins or mRNAs. Essential genes are expressed at higher levels, so that cells have at least one molecule of a protein that they cannot live without. These numbers may be counterintuitive, but they generally conform to earlier ensemble measurements (*6*). What is truly intriguing is the high level of noise in gene expression that the researchers discovered across the whole genome.

For low-abundance proteins (<10 copies per cell), the level of noise decreased as abundance increased. For more abundant proteins, the noise level remained stationary above a certain limit. One component of this noise—dubbed "intrinsic" noise—arises because a cell typically holds just one copy of each gene and very few molecules of gene-activating proteins. Under such conditions, the interaction of the two is subject to chance, resulting in stochastic (random) synthesis of mRNA and protein (*7*). Although intrinsic noise nicely explains noise trends in low-abundance proteins, it is not obvious why noise does not continue to decrease as proteins become more abundant. One hypothesis is that cells have variable "metabolic capacities" to produce proteins, perhaps due to variations in the number of RNA polymerases, ribosomes or other factors that globally affect the synthesis of proteins. These factors—called "extrinsic" noise—might create a floor below which noise levels do not fall (*5*, *8*, *9*). One prediction generated by this hypothesis, confirmed by Taniguchi *et al*., is that the levels of two proteins subjected to extrinsic noise will fluctuate over time in a correlated manner.



Noisy inheritance. For a given gene, the number of molecules of mRNA (red dots) and corresponding protein (yellow dots) can vary greatly among genetically identical cells in a population at a given moment in time. This high level of "noise" is due, in part, to differences in the life spans of mRNAs, which are relatively short-lived, and proteins, which can persist for longer than the time required for cell division. Surviving protein molecules are passed to daughter cells by random assortment, resulting in unequal distribution when the number of molecules of a protein is small. As a result, some cells have many copies of mRNA and proteins for a given gene, whereas other cells can have relatively few or none, and the number of mRNAs and proteins within a cell may not correlate.

A striking observation is that, although the numbers of molecules of mRNAs and proteins for any given gene correlate well at the ensemble level, they do not correlate at all within individual cells. How is it that, in an organism in which the processes of transcription and translation are coupled, the number of mRNAs does not relate to the number of proteins within each cell? The explanation lies in the different lifetimes of mRNAs and proteins. The mRNAs survive for only a few minutes within cells, whereas proteins persist for hours—exceeding the duration of the cell cycle (*5*, *10*). Furthermore, for many cells the only source of some proteins is those that are inherited from the mother cell, as mRNA is produced relatively rarely (see the figure). This results in unequal inheritance of the limited number of molecules of a given protein

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during cell division (*8*, *10*), a phenomenon that also occurs in mammalian cells (*11*).

Another consequence of differences in the lifetimes of mRNAs and proteins is that noise is higher for mRNAs than it is for their corresponding proteins. The mRNAs are produced in short random bursts and degrade soon after being used as templates for the synthesis of a few protein molecules, whereas the synthesized proteins are added to a pre-existing pool. Protein levels are thus relatively "buffered" from fluctuations in the level of the corresponding mRNA. Similar buffering has been observed in mammalian cells (*12*).

Are there any differences in noise characteristics between bacteria and eukaryotes? Investigators have performed a pair of genome-wide studies in yeast (*4*, *9*) that are similar to the study reported here. A comparison of the results suggests that gene expression in bacteria is noisier than in yeast (*5*). Although researchers have yet to perform a genome-wide study of higher eukaryotes, the results of several studies with reporter genes and with natural genes suggest that mRNA expression in mammalian cells is noisier than in both yeast and bacteria (*2*). A possible reason is that, in the higher eukaryotes, the control regions of genes are sequestered within tightly packed chromatin and the gene activating proteins can gain access to these regions only during random episodes in which local chromatin becomes loose (*12*).

Now that there is reliable knowledge of the levels of expression and the underlying variation of mRNAs and proteins for a considerable portion of the *E. coli* genome, it is possible to explore how noise propagates along gene expression pathways, in which the amount of one protein can influence the expression of another. Investigators can also investigate how cells coordinate the expression of proteins that need to work together, such as multisubunit proteins or proteins that serve within metabolic cycles. Genome-wide studies of noise in related organisms, or in the same organism under different conditions, such as stress or aging, will allow researchers to determine whether noise is simply a limitation of the gene expression apparatus or an essential trait subject to evolutionary selection and refinement.

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PLANETARY SCIENCE

Winds of Change on Titan

Periodic strong winds blowing opposite to the prevailing wind may explain the dune orientation on Titan.

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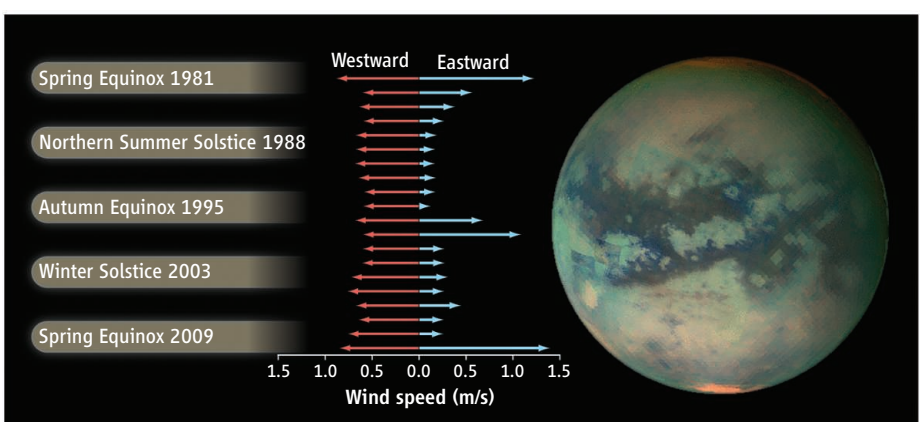
On Saturn's moon Titan, giant sand dunes cover more than 20% of the surface. The orientation of thousands of dunes (*1*, *2*) within Titan's equatorial belt indicates transport of sand from west to east (by "westerly" winds), whereas all the atmospheric circulation models suggest that the winds should be in the opposite direction. A new model by Tokano (*3*) may have found the resolution: Although the winds are usually easterlies (as in other work), there is a blast of wind from the west for a brief interval around each equinox, and it is these stronger winds that dominate the dune orientation.

The discovery of dunes on Titan (*4*) in Cassini radar imagery was itself something of a surprise (and only possible because Titan's dunes are so large—a kilometer or so wide, tens to hundreds of kilometers long, and often more than 100 m high), and it is not clear where all this sand comes from. The term "sand" in geology is a particle size range (0.06 to 2 mm), not a composition. For example, dunes on Earth and Mars are not always made of quartz sand; there are the black basaltic sands of Hawaii and Iceland, or the white sands of gypsum in New Mexico; Mars has these too, plus some striking green sands of olivine. On Titan, the dark dune sands make up an inventory (*5*) of ~0.5 million km^3 of material—apparently of an organic composition, as spectroscopic mapping (*6*) by Cassini's infrared spectrometer shows a signature, concentrated in the sand, of aromatic molecules such as benzene. This makes the dunes the largest carbon sink on Titan (larger than the polar seas of liquid hydrocarbons, and 1000 times the carbon in all the coal known on Earth). The dune organic inventory com-



Going against the flow. The annual range of near-surface equatorial zonal winds on Titan in Tokano's model (*3*): The strongest westerly (eastward) wind in an interval is shown as a blue arrow, the strongest easterly in red. The winds are predominantly easterlies, and if the sand transport threshold were as low as 0.5 m/s, easterlies would drive the dune orientation. However, if the threshold is higher (e.g., 1.0 m/s), only the westerlies at equinox are fast enough to form dunes, which therefore indicate this direction even though easterlies are more common overall.

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