This finding is particularly important for car manufacturers attempting to replace current steel engine block materials (as is still the case for heavy-duty engines) with lighter alloys that contain considerable amounts of aluminum or magnesium.

It was previously known that the ZDDP tribofilm is not only self-limiting in thickness but also features a gradient in composition, structure, and mechanical properties that becomes stronger and stiffer nearer the substrate (*6*). The formation of this complex structure can now be elegantly explained with the observed contact-pressure dependence of tribofilm formation. The tribofilm has a lower modulus than the substrate, so the contact stress at constant load decreases as the tribofilm thickens, which in turn reduces the amount of stress-induced cross-linking and other reactions that produce the tribofilm. Weaker, more compliant structures form that lead to a gradually further reduction in contact pressure, which ultimately terminates any further growth.

Considering the large numbers of internal combustion engines in service, even small improvements in engine efficiency, emission levels, and durability have a major effect on the world fuel economy and the environment, with a potential to save tens of billions of liters of fuel annually (see the figure) (*10*). The innovative in situ approach demonstrated by Gosvami *et al.* has the potential to transform lubrication science if researchers can successfully apply it to the multitude of molecular-level tribochemical phenomena that still lack detailed understanding. Given a nanometer-scale understanding of the chemistry of lubricants and how additives affect the interactions between lubricants and rubbing surfaces, new lubricants could be designed that will be longer-lasting, environmentally friendly, and compatible with catalytic converters and lightweight nonferrous engine block materials alike. ■

REFERENCES AND NOTES

1. D. Dowson, *History of Tribology* (Longman, London, 1979).
2. R. M. Mortier, M. F. Fox, S. T. Orszulik, Eds., *Chemistry and Technology of Lubricants* (Springer-Verlag, Dordrecht, Netherlands, ed. 3, 2010).
3. S. M. Hsu, *Tribol. Int.* **37**, 553 (2004).
4. N. N. Gosvami *et al.*, *Science* **348**, 102 (2015).
5. S. C. Tung, M. L. McMillan, *Tribol. Int.* **37**, 517 (2004).
6. H. Spikes, *Tribol. Lett.* **17**, 469 (2004).
7. H. Spikes, *Lubricat. Sci.* **20**, 103 (2008).
8. A. M. Barnes, K. D. Bartle, V. R. A. Thibon, *Tribol. Int.* **34**, 389 (2001).
9. M. A. Nicholls, T. Do, P. R. Norton, M. Kasrai, G. M. Bancroft, *Tribol. Int.* **38**, 15 (2005).
10. K. Holmberg, P. Andersson, A. Erdemir, *Tribol. Int.* **47**, 221 (2012).

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GENE EXPRESSION

MicroRNAs silence the noisy genome

Evolution may have selected for a dampening service for genes whose noise may have otherwise been too high

By **Yonit Hoffman**[1,2] *and* **Yitzhak Pilpel**[1]

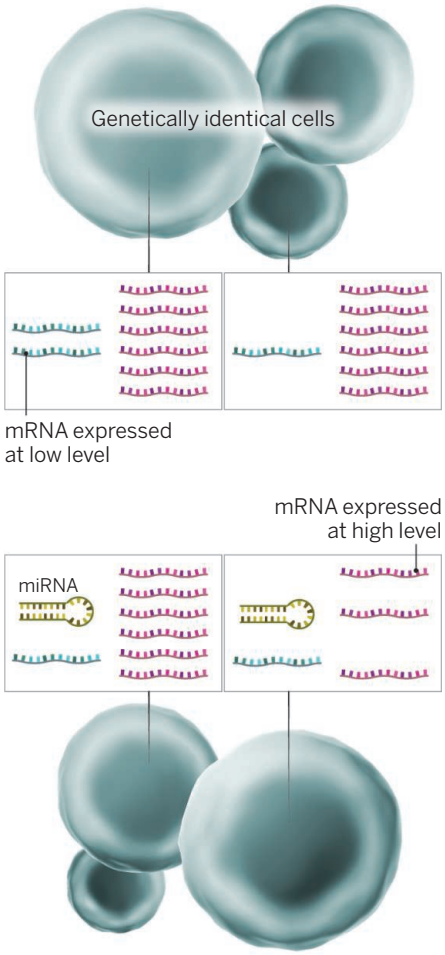
All molecular machines have imperfections, and the biological ones are no exception. One type of flaw is a quantitative one: Although all the cells within an organ are genetically identical, the concentrations of many of their proteins can be "noisy"—that is, vary and fluctuate between all the cells. Biologists decompose such noise into two sources: an intrinsic one, which results from the stochastic nature of the biochemistry operating within cells, and an extrinsic one that manifests global differences between cells, such as the number of protein production facilities (e.g., ribosomes) (*1*). A major question is whether organisms have evolved means to control noise, especially when imprecisions are detrimental. On page 128 in this issue, Schmiedel *et al.* (*2*) report combining mathematical modeling and a synthetic gene approach to establish a complex role for microRNAs (miRNAs) in controlling cellular protein content.

Since their discovery, miRNAs have been considered important regulators of basic cellular and organismal biology. These small noncoding RNAs base pair with complementary sequences in messenger RNAs (mRNAs), thereby degrading their mRNA targets or preventing their translation into proteins. Yet, the observation that the quantitative effect of miRNAs on their targets is often minor remains a mystery. It has thus been suggested that miRNAs provide noise filtration functions, limiting variability in protein expression across a population of cells (*3*, *4*). But how can one reveal the potential noise-reducing effect of miRNAs on genes? A mere inspection of genes within their natural complex genomic context might not suffice because this context consists of numerous variables and it is impossible to dissect the effects of each of them. Schmiedel *et al.* avoid these obstacles by analyzing a reporter gene that is synthetically connected to gene parts that convey regulation by miRNA. In particular, the authors constructed a fluorescence reporter that allows measuring of gene expression noise, while varying miRNA regulatory input. In this approach, miRNAs bind to targeted mRNAs through dedicated regions—the 3′-untranslated regions (UTRs) of the mRNAs. Sequences that contain different 3′UTRs, each with one or more binding sites (of varying binding strengths) for different miRNAs, were synthesized. These sequences were each fused to the fluorescent reporter gene. Each construct was then expressed in cultured mammalian cells (including constructs with no binding site for miRNAs).

> ***"Which genes should be the prime subjects of such a noise dampening mechanism?"***

Comparing single-cell fluorescence revealed an important difference between reporters that have or that do not have miRNA binding sites. In cells that happened to express the reporter at a low level, noisiness of its expression dropped if the reporter had a miRNA binding site. By contrast, in cells that expressed the reporter at a high level, the presence of a miRNA binding site was associated with elevated noisiness of its expression (see the figure). This result was recapitulated by a mathematical model that implements basic principles of gene expression, with clear predictions: Reduction in intrinsic noise should be proportional to miRNA-mediated repression, and extrinsic noise will be "inherited" from noise in the miRNAs (there is variability in the expression of miRNAs as well). To test the intrinsic noise prediction, Schmiedel *et al.* created another reporter, subject to the same miRNA regulation. Because mRNAs encoding both reporters "see" the same miRNAs, differences between their noise must be ascribed to the intrinsic compo-

[1]*Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.* [2]*Molecular Cell Biology, Weizmann Institute of Science Rehovot, 76100 Israel.*
E-mail: pilpel@weizmann.ac.il



Noise-canceling RNA. The amounts of mRNA corresponding to two genes are shown in two identical cells. One gene is expressed at a low level, and there is variation (noise) of this expression between the cells. In the presence of a regulatory miRNA, the mRNA that is expressed at a lower level fluctuates less, whereas the mRNA that is present in greater amounts becomes more noisy.

nent. For each reporter, the authors synthesized a version encoding a 3′UTR with or without binding sites for miRNA. The result was clear: miRNA reduced intrinsic noise, even when the reporter was expressed at a high level. This suggests that the original observation—that there is increased noise of a gene's expression when its expression level is high—must have been due to extrinsic noise.

Indeed, as for the extrinsic noise, Schmiedel *et al.* suspected that modifying the noise level of the miRNAs themselves would affect the reporter's noise too. For that, the authors examined what happens if the miRNA is produced from two gene copies, rather than from one. This situation could reduce noise in the miRNA because fluctuations in the expression of one copy are counteracted by the other. They found that miRNAs encoded by more than one gene copy in the genome presented less noise. Further, mRNAs of natural genes are often targeted by more than one type of miRNA. Schmiedel *et al.* determined that such combinatorial effects reduce the amount of the extrinsic noise because it decreases the total amount of miRNA-pool noise. This finding was found to hold also for native genes' 3′UTR.

A key question in any such synthetic approach is, how applicable are the conclusions to natural genes? Examining expression for the entire mouse genome, Schmiedel *et al.* reveal that some 90% of the genes fall within the range of expression that would subject them to such a miRNA-based noise dampening mechanism.

Which genes should be the prime subjects of such a noise dampening mechanism? Single-cell transcriptomics (*5*, *6*) should allow noise measurement for each gene and miRNA. With such data, it will be possible to examine the connection between the extent of miRNA regulation of a gene and its noise. Means to manipulate miRNA levels (*7*) should allow examination of the effect of changes in miRNA expression on the noisiness in their targets. One can then ask which genes are endowed with noise filtration and whether there are genes that are deliberately noisy. Schmiedel *et al.* ascribed intrinsic noise reduction to enhanced transcription that presumably compensates for the mRNA degradation (which maintains a given expression level). Recent reports on the "circular" nature of gene expression—namely, that mRNA degradation feeds back to elevate transcription (*8*)—may thus provide an intriguing potential mechanism that explains the intrinsic noise reduction effect. And the story need not end with miRNAs. A most profound revolution in genomics is the realization that there are many additional types of RNA. For instance, "antisense" RNAs may also act in noise filtration, especially when coregulated with their corresponding sense transcript (*9*). Perhaps some long noncoding RNAs (*10*), too, contribute to fine tuning of gene expression programs. ■

REFERENCES

1. M. B. Elowitz, A. J. Levine, E. D. Siggia, P. S. Swain, *Science* **297**, 1183 (2002).
2. J. M. Schmiedel *et al.*, *Science* **348**, 128 (2015).
3. E. Hornstein, N. Shomron, *Nat. Genet.* **38** (suppl.), S20 (2006).
4. M. S. Ebert, P. A. Sharp, *Cell* **149**, 515 (2012).
5. D. A. Jaitin *et al.*, *Science* **343**, 776 (2014).
6. T. Hashimshony, F. Wagner, N. Sher, I. Yanai, *Cell Rep.* **2**, 666 (2012).
7. J. Krützfeldt *et al.*, *Nature* **438**, 685 (2005).
8. G. Haimovich *et al.*, *Cell* **153**, 1000 (2013).
9. M. Lapidot, Y. Pilpel, *EMBO Rep.* **7**, 1216 (2006).
10. M. Guttman *et al.*, *Nature* **458**, 223 (2009).

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PSYCHOLOGY

Infants explore the unexpected

Infants are more likely to explore objects that behave in unexpected ways, such as passing through walls

By **Laura Schulz**

Science can delight us with new and surprising findings. Sometimes, however, a study delights us by confirming something we already believed but could not yet prove. This is the kind of pleasure occasioned by Stahl and Feigenson's report on page 91 of this issue (*1*). In a series of elegant experiments, the authors show that, controlling for overall attention, 11-month-old infants are more likely to learn a new sound associated with an object if the object previously violated the infants' expectations (e.g., by appearing to pass through walls or roll over gaps without falling) than if the object behaved as expected. Moreover, infants not only selectively explore objects that violate their expectations but also explore in ways specific to the violation. Thus, they bang objects that violate expectations of solidity and drop objects that violate expectations of support (see the figure).

Perhaps the most surprising thing about these findings is that they have not observed made sooner. For decades, researchers have known that infants look longer at events that violate their expectations than at events consistent with their prior beliefs (*2*). The presumption was that such selective attention must support learning, but it was difficult to show this in a way that did not follow trivially from the fact that infants look for a long time at unexpected events. The current study solves that problem by matching infants' initial exposure to the events and then asking whether infants who observe theory-violating evidence are more likely to learn an unrelated property of the objects.

Researchers have also long assumed that children's exploratory play must support learning (*3*–*5*). Again, however, it has been difficult to demonstrate this in a way that does not follow trivially from the fact that the longer children explore an object,

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