The authors[1] used transcriptional reporters — in which a second copy of the gene of interest drives the expression of a fluorescent protein — to follow variations in gene expression in live worms. A key requirement of this approach (verified by the authors) is that fluctuations in expression of the reporter accurately reflect fluctuations in expression of the endogenous genes. This means that the reporter is tracking expression noise resulting from differences in cellular environment — extrinsic noise[3] — rather than the random turning on and off of individual promoters.

Lehner and co-workers first investigated why mutations in the T-box transcription factor gene *tbx-9* that completely abolish the gene's function cause an incompletely penetrant defect in *C. elegans* larval development: roughly half of the animals lacking *tbx-9* develop normally; the other half have muscle and epidermal defects. The authors observed that overexpression of *tbx-8* — a gene closely related to *tbx-9* — eliminates the defects caused by loss of *tbx-9*. What's more, loss of *tbx-9* in their mutants caused upregulation of *tbx-8*.

More strikingly, the authors observed that differences in *tbx-8* expression were a strong predictor of the phenotypic effects of *tbx-9* loss — *tbx-9*-mutant worms that expressed *tbx-8* at a low level were considerably more likely to develop abnormally than were genotypically identical individuals that expressed *tbx-8* more strongly. Thus, stochastic differences in the feedback loop that compensates for *tbx-9* loss by upregulating *tbx-8* contribute to the variable penetrance of the *tbx-9* mutation. Lehner and colleagues observed a similar set of effects with the transcription factors *flh-1* and *flh-2*, which, like *tbx-8* and *tbx-9*, are a pair of related genes that resulted from ancient gene duplication. This type of noisy feedback between related genes may therefore be quite common.

Although these findings represent a step forwards, the variability of *tbx-8* expression could not fully account for the variable penetrance of the *tbx-9* mutation. What, then, is the source of the remaining variability? Molecular chaperones — proteins that assist other proteins in folding — can buffer a wide range of cellular defects, especially the Hsp90 chaperone[4] (also known as DAF-21 in *C. elegans*). Lehner and co-workers therefore investigated random fluctuations in chaperone levels in individual worms as a possible explanation of the missing variability. They found that fluctuations in expression of *daf-21* were a strong predictor of the effects of *tbx-9* loss. Importantly, the effects of the differences in *tbx-8* and *daf-21* expression were independent of each other but synergistic: more than 90% of worms with high levels of *daf-21* and *tbx-8* expression developed normally, whereas roughly two-thirds of the animals in which expression of both genes was low did not.

Lehner and colleagues found that the observed variability in penetrance of *tbx-9* loss in their study can, to a remarkable degree, be accounted for by variations in expression of *tbx-8* and *daf-21*. This, in turn, raises the question of what underlying mechanisms in the cell cause the observed variability and how many other genes are affected by these fluctuations. In the case of *daf-21*, the authors show that the fluctuations are probably part of coordinated changes in the expression of a broad range of chaperone genes, including one known as *hsp-4*. Such 'noise regulons' — synchronized stochastic changes in functionally related genes — are particularly suitable for causing coordinated effects on cell physiology, because the related genes act together to carry out common functions[5] (Fig. 1). However, the authors did not find evidence that fluctuations in *tbx-8* expression correlate with variations in the expression of chaperones, and it may be that there are no other genes whose noise co-varies with that of *tbx-8*. A more tantalizing possibility is that variations in the expression of *tbx-8* also reflect a coherent cellular state in which other members of the *tbx-8*/*tbx-9* pathway fluctuate in unison. This raises the further question of how many such noise regulons exist, and what controls their activity.

More broadly, it is clear from recent studies[1,2] that stochastic fluctuations can have a big impact on the penetrance of gene alleles. A better understanding of the structure of noise — which genes tend to fluctuate together, and how these fluctuations are controlled — should provide crucial insight into the nature of the genotype–phenotype relationship. ■

Hana El-Samad *is in the Department of Biochemistry and Biophysics, and* **Jonathan S. Weissman** *is in the Department of Cellular and Molecular Pharmacology, University of California, San Francisco, San Francisco, California 94158, USA. J.S.W. is also at the Howard Hughes Medical Institute.*
e-mails: hana.el-samad@ucsf.edu; weissman@cmp.ucsf.edu

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MATERIALS SCIENCE

A sense for touch

Will a sense of touch similar to that of humans ever be developed in robots? Results on the physics of friction for fingerprint-like ridges sliding across textured surfaces may lead the way to tactile robotic sensors.

C. MATHEW MATE & ROBERT W. CARPICK

When we rub a finger across a surface, our sense of touch is remarkably adept at distinguishing between different textures[1]. For example, astute clothes shoppers can easily feel the difference in texture between cotton and lower quality polyester fabrics, just as experienced cashiers can spot counterfeit banknotes from the feel of the paper. Writing in *Physical Review Letters*, Wandersman *et al.*[2] provide a major advance towards understanding the physics behind these tactile sensations, showing how a modulated frictional signal is generated by fingerprint-like ridges rubbing against the roughness of an opposing surface. This improved understanding of the relationship between friction and surface textures should have an impact in many areas, but particularly in the field of tactile sensors for robotic design. Incorporating sensors capable of mimicking the human sense of touch has long been recognized[3] as important for improving the ability of robots to grasp objects firmly without damaging them.

Wandersman *et al.*[2] present measurements and analysis of the tangential or friction force generated as a rubbery elastomer block with periodic surface ridges slides over a rough glass surface. The ridges on the elastomer surface, which have periods ranging from 125 to 760 micrometres, serve as stand-ins for the epidermal ridges on human fingers (Fig. 1a). They show that, when pressed against the glass surface to form contact regions several millimetres in diameter, the elastomer deforms around the rough surface texture in the same way as the epidermal ridges would if pressed against such a surface.

With numerous ridges in contact, one might expect that any periodic variation in the friction force due to these ridges would average out; indeed, this can be shown analytically if the friction force generated in each microscopically small area in contact (much smaller than the width of a ridge) is strictly proportional to the local normal or loading force pressing the two surfaces into contact over this area. This linear relationship between the friction and load forces is usually referred to as Amontons' law of friction[4], which states that the friction force, F, is proportional to

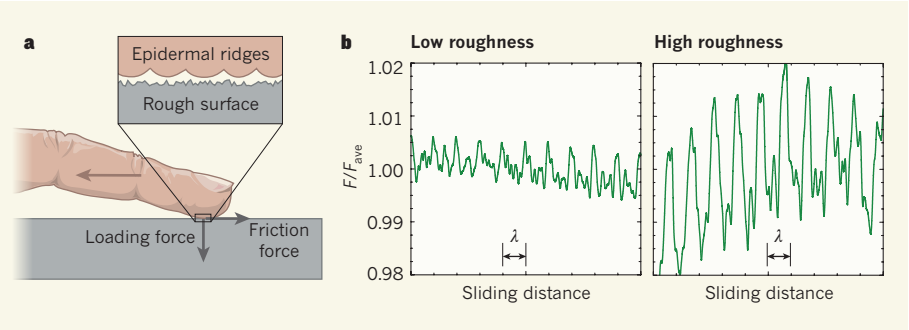

Figure 1 | The friction force. **a**, When a fingertip is rubbed against a rough surface, the net friction force acting on the epidermal ridges increases with the loading force that the finger exerts on the ridges to press them into contact with the surface. **b**, Wandersman *et al.*[2] measure the net friction force that acts on an elastomer block as it slides against glass surfaces of differing roughness. The elastomer block has ridges similar in structure and elasticity to the epidermal ridges on a finger. Shown here is the instantaneous friction force F, normalized to the average friction force F_{ave}, as a function of sliding distance. λ is the spacing of the ridges on the elastomer block and is 218 micrometres. The force has a slight oscillating component that has the same period as the separation between the ridges and increases with the degree of roughness on the glass. (Part **b** modified from ref. 2.)

the loading force, L, or $F = \mu L$, where μ is the coefficient of friction. However, the authors find that, rather than this friction modulation averaging to zero, the net friction acting on the elastomer block goes up and down slightly (by up to a few per cent) during the sliding experiments (Fig. 1b), with the same period as the ridges. And, surprisingly, the amplitude of this modulation actually increases when the net loading force increases.

One of the fundamental advances provided by Wandersman *et al.*[2] is their analysis showing that, if the local friction coefficient depends even slightly on pressure (which is equivalent to friction being slightly non-linear with load), the modulation in friction can increase with loading force. They find good agreement between the experiments and a model in which friction varies non-linearly with load: $F = AL^{\gamma}$, where $\gamma = 0.87 \pm 0.04$ and A is a constant. In this model, the roughness of the surface against which the fingerprint-like ridges are being slid has the important role of providing a heterogeneous distribution of contact pressure locally along the ridges. As the roughness increases, a wider distribution of loading pressure occurs, leading to a larger modulation in friction as a result of the non-linear nature of friction with load. The spatial period of the ridges serves to concentrate the minute variation of friction caused by these texture-induced pressure modulations all at one frequency, making it much easier to discern this variation from the average net friction.

The sliding of fingerprint-like ridges over surfaces is not the only area in which Wandersman and colleagues' analysis should apply. Because friction forces are rarely strictly linear with loading forces (as postulated in Amontons' law)[5], we believe that this analysis could provide a valuable way to use friction fluctuations to characterize surface roughness on many types of material pairs sliding against each other. The amplitude and the load-dependence of the fluctuations reveal information on the surface's topographic characteristics at length scales much smaller than that of the patterned ridges. As a result, we think that one exciting area to which the method developed by Wandersman *et al.*[2] could be extended is the characterization of surface roughness down to the nanometre scale or even smaller atomic length scales.

For example, for many years, atomic-scale modulations of friction have been observed when the sharp tip of an atomic force microscope (AFM) slides across the periodic arrangement of atoms on a crystalline surface[6]. However, these AFM experiments typically require very small loading forces (nanonewtons) to maintain a contact area of only a few nanometres in diameter in order to see the atomic-scale modulation of friction. But, perhaps, with suitably designed patterned ridges and friction sensors, this ability to sense the atomic-level contribution to the friction modulation could be extended from the current nanometre-sized contact zones of AFMs to millimetre-sized contact zones, allowing future robotic fingers to feel the atomic-level contribution to surface texture. ■

C. Mathew Mate *is at the Hitachi San Jose Research Center, San Jose, California 95135, USA.* **Robert W. Carpick** *is in the Department of Mechanical Engineering and Applied Mechanics, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.*
e-mails: mathew.mate@hitachigst.com; carpick@seas.upenn.edu

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CANCER

Sacrifice for survival

Cancer cells ignore oxygen availability, opting for less efficient, anaerobic ways of generating energy. The wisdom behind this choice seems to be in preventing the accumulation of reactive oxygen species, and so oxidative damage.

NANA-MARIA GRÜNING & MARKUS RALSER

When oxygen is plentiful, cells convert glucose to energy through the consecutive processes of glycolysis and oxidative respiration. However, cancer cells exhibit what is known as the Warburg effect: even in the presence of oxygen, they prefer the much less efficient process of glucose fermentation for energy production[1]. This seems counter-intuitive because rapid cell proliferation, which is required for tumour growth, has high energetic demands[2,3]. In a paper published in *Science*, Anastasiou and colleagues[4] provide evidence that cancer cells undergo this metabolic shift to clear reactive oxygen species (ROS) and so prevent oxidative damage. Thus, reconfiguration of the central carbon metabolism to counteract oxidative stress seems to be a major prerequisite for cancer progression.

Textbooks offer two possible explanations for the decline in respiratory activity during cancer development. First, with the increase in nucleotide and macromolecule biosynthesis, there is a shortage of carbon equivalents for oxidative respiration. Second, a higher speed of glycolysis makes anaerobic metabolism more efficient, with more lactate being generated from pyruvate, the end product of glycolysis; this allows cancer cells to feed each other by shuffling lactate[2,3].

Neither hypothesis fully explains the metabolic reconfiguration in cancer cells. For one,