

in the spotlight: can our excited synapses comprehend them? ■

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- McCabe, B. D. *et al.* *Neuron* **39**, 241–254 (2003).
- Haghighi, A. P. *et al.* *Neuron* **39**, 255–267 (2003).
- DiAntonio, A., Petersen, S. A., Heckmann, M. & Goodman, C. S. *J. Neurosci.* **19**, 3023–3032 (1999).

- Kazama, H., Morimoto-Tanifuji, T. & Nose, A. *Neuroscience* **117**, 615–625 (2003).
- Aberle, H. *et al.* *Neuron* **33**, 545–558 (2002).
- Marques, G. *et al.* *Neuron* **33**, 529–543 (2002).
- Petersen, S. A., Fetter, R. D., Noordermeer, J. N., Goodman, C. S. & DiAntonio, A. *Neuron* **19**, 1237–1248 (1997).
- Lisman, J., Schulman, H. & Cline, H. *Nature Rev. Neurosci.* **3**, 175–190 (2002).
- Turrigiano, G. G. & Nelson, S. B. *Curr. Opin. Neurobiol.* **10**, 358–364 (2000).
- Davis, G. W. & Bezprozvany, I. *Annu. Rev. Physiol.* **63**, 847–869 (2001).

Materials science

Molecules squeezed and stroked

Steve Granick, Zhiquan Lin & Sung Chul Bae

Soft matter is often found in tight spots. A study shows that tangled chain-like molecules, squeezed between solid surfaces and stroked by sliding, might become exceptionally ordered.

How does a pen write on paper? As you blink your eyes, how do tears lubricate your cornea? As you type, how does the hard disk store information? All of these apparently disparate actions share a central feature — surfaces, separated by fluids, are squeezed together and the molecules sandwiched between are stroked by sliding. Sliding is one of the most common processes of the everyday world, but we know little about the interplay between surfaces and their confined lubricants.

Shinji Yamada has now looked at the effect of sliding on the behaviour of the silicone oil polymer PDMS — a flexible threadlike chain molecule that normally exists in a tangled, randomly coiled form. Writing in *Langmuir*¹, he reports that the degree of friction between two sliding surfaces depends on the number of layers of PDMS sandwiched between. Remarkably, each layer is the width of the polymer backbone, indicating that sliding might have ordered the polymer chains.

To look at the behaviour of confined PDMS during sliding, Yamada sandwiched a film of the polymer between two layers of solid mica. He then measured the kinetic friction produced as the two surfaces were squeezed and simultaneously slid over one another. Surprisingly, he was able to compress the confined molecular film during squeezing and sliding to thicknesses equalling only two, three or four molecular layers. And the number of layers affected the total friction between the sliding surfaces. When the polymer was squeezed to a thickness of three or four molecular layers, the middle layers also seemed to slide, resulting in low friction. But when the thickness of the film was squeezed to the width of only two molecular layers, the degree of friction increased abruptly by six to eight times (Fig. 1).

The finding that PDMS can form such thin layers in films is surprising, because

decades of research have led to the view that long-chain polymers form much thicker conformations — instead of aligning in flat layers they coil randomly, rather like tangled spaghetti². The polymer that Yamada looked at is about 1,000 repeat-units long, so, if it forms a random coil, the polymer film should be about 10 nm thick. But Yamada describes PDMS films that were an order of magnitude thinner than this.

A speculative but plausible explanation for this discrepancy is that sliding might have oriented the polymer chains into discrete molecular layers, each layer having the thickness of the polymer backbone (Fig. 1). Extreme deformations are most likely to happen in thin films of soft materials because the movements of these molecules are retarded by confinement and so they are deformed more rapidly than they can re-equilibrate³. The difference between polymers at rest, or at equilibrium, and polymers

undergoing deformation during sliding, is considerable.

Why are studies such as Yamada's important? If the model shown in Fig. 1 is correct, measuring the increases in friction under different degrees of compression could provide clues about how precisely a polymer is oriented by sliding. Studies of confined molecules might also have more practical implications. The ability to manipulate giant molecules under confinement may enable new kinds of nanoscale structures to be fabricated. For example, the use of conducting polymers in display devices has been limited by an inability to produce sufficient order along the polymer backbones⁴. If sliding can orient other large polymers, besides PDMS, the technique described by Yamada might be a useful route towards enhancing order in thin films of these technologically useful molecules.

But how might sliding orient giant polymers? Computer simulations and theory provide clues⁵ but no definite answers. Imaging the local density of molecules in ultrathin films and the local orientation of individual chain segments are technical hurdles that must be overcome before these questions can be answered. The most advanced synchrotron X-ray-reflectivity measurements have begun to yield images of confined molecules at rest⁶ but not yet during sliding. The interaction of visible light with matter⁷ — for example, Raman and infrared imaging — has impressive potential, but this technology is at an early stage. The problem with using these techniques to image confined molecules is distinguishing the signal (the fluid monolayer) from all the noise (the sliding surfaces and the solids beneath them).

Another task will be to distinguish the behaviour of individual confined molecules from the average behaviour. Biophysics has been invigorated by single-molecule

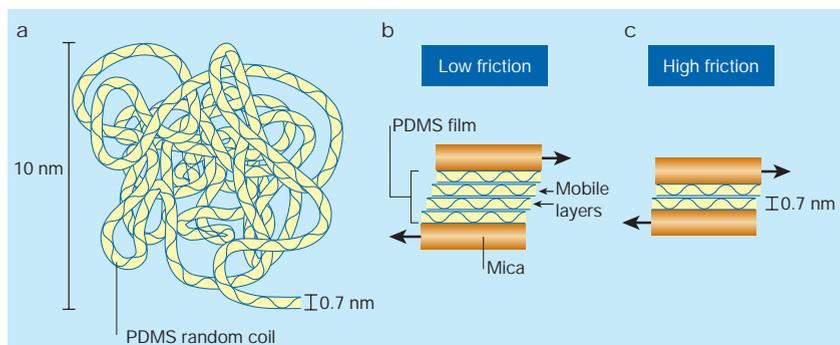


Figure 1 Squeezing out the tangles. **a**, The polymer PDMS usually exists in a random coil conformation. **b**, **c**, Yamada¹ has shown that PDMS might be ordered into discrete molecular layers — each layer the width of the polymer backbone — by sliding when it is confined between two atomically smooth mica surfaces. Compressing the sandwiched film to a thickness of four backbone widths produces low friction between the sliding surfaces, as the middle layers are mobile. When the film is compressed to a thickness of two backbone widths, the magnitude of friction abruptly increases. A challenge for materials scientists is to augment the macroscopic friction measurements with local measurements of molecule density, alignment, mobility and energy flow between chemical bonds as the molecules slide.

approaches to studying processes such as enzyme turnover. Applying a single-molecule approach to thin films of soft matter, one study showed that the average friction masked an unexpected variety of molecular movement⁸.

Yamada¹ has provided a conceptual model of how sliding might order large polymer backbones. The challenge now is to put flesh on this model by revealing the mechanisms underlying this phenomenon. The word friction evokes the triviality of changing the oil in one's automobile, yet, as David Tabor emphasized ten years ago⁹, a fundamental issue must be addressed before we can fully understand friction and sliding — how is energy dissipated when surfaces slide over one another? What is the roadmap of energy flow as molecules slide past one another? When these questions are answered, the word 'friction' will have real substance, and models of friction will be

predictive. Then we will have to apply our understanding of friction to issues such as biolubrication¹⁰. Machinery wears out, as we all know. So do eyes and knees. ■

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1. Yamada, S. *Langmuir* **19**, 7399–7405 (2003).
2. Jones, R. A. L. & Richards, R. W. *Polymers at Surfaces and Interfaces* (Cambridge Univ. Press, 1999).
3. Granick, S. *Phys. Today* **52**, 26–31 (1999).
4. Scherf, U., Riechel, S., Lemmer, U. & Mahrt, R. F. *Curr. Opin. Solid State Matter Sci.* **5**, 143–154 (2003).
5. Bhushan, B., Israelachvili, J. N. & Landman, U. *Nature* **374**, 607–616 (1995).
6. Seeck, O. H. et al. *Europhys. Lett.* **60**, 376–382 (2002).
7. Salmeron, M. *Tribol. Lett.* **10**, 69–79 (2001).
8. Mukhopadhyay, A., Zhao, J., Bae, S.-C. & Granick, S. *Phys. Rev. Lett.* **89**, 136102 (2002).
9. Tabor, D., Singer, I. L. & Pollack, H. M. (eds) *NATO Advanced Study Institute on Fundamentals of Friction* (Kluwer, Dordrecht, 1992).
10. Zhu, Y. & Granick, S. *Macromolecules* **36**, 973–976 (2003).

Developmental biology

Partners united

Matthew Freeman

There is often more than one way of cracking a scientific problem. Two views of one question have led to the marriage of two signalling proteins in search of a partner.

The world would be less interesting if unicellular organisms in some ancient swamp had not teamed up, giving rise to multicellular species and, eventually, to us. But, at the same time as allowing new survival strategies (not to mention the emergence of civilization), the evolution of multicellularity presented new difficulties: for example, cells in a single organism, and therefore derived from the same egg and sperm, had to choose for the first time between many possible fates.

We now know that most cells learn their fate from signals produced by other cells, and the hunt is on to identify components of these signalling systems. On pages 507 and 512 of this issue, Weiss, Frasch and co-workers¹ and Palmer and colleagues² describe experiments that unite a pair of hitherto enigmatic signalling proteins — a secreted protein, Jeb, and a cell-surface-located receptor, Alk. By showing that Jeb binds to and activates Alk, these papers provide new insight into development, and also illustrate the relationship between development and cancer: developmental signals are potent regulators of cell behaviour, and so can have disastrous effects if uncontrolled.

This story began in 1997, when unregulated activity of the anaplastic lymphoma kinase (Alk) protein was discovered to be the cause of a cancer known as anaplastic large-cell lymphoma^{3–5}. Alk belongs to a family

of enzymes called receptor tyrosine kinases, and is most closely related to the insulin receptor. So it was straightforward to predict — and it was subsequently confirmed — that, like other members of this enzyme family, Alk is a cell-surface receptor that activates several intracellular signal-transduction cascades, including a pathway that contains the so-called mitogen-activated protein (MAP) kinase. It was, however, much harder to determine which protein (or proteins) binds to Alk to activate these pathways.

Simultaneously, but in apparently unrelated experiments, fruitfly biologists were

trying to understand how the intricate patterning of the embryonic musculature develops. Scott and colleagues⁶ had identified an unusual secreted protein, Jelly belly (Jeb), which was required for the development of the visceral muscles — those that are under involuntary control, such as the muscles that move food through the gut. They found that Jeb was emitted from adjacent somatic muscles, and proposed that it was a signal by which somatic muscles could induce neighbouring mesoderm tissue to produce visceral muscle cells.

In a collaborative effort, the laboratories of Manfred Frasch and Joseph Weiss have pursued this model, as they now describe¹. They examined fruitfly embryos with mutations in the *jeb* gene, and discovered that Jeb is required specifically for the formation of visceral 'founder' cells in mesoderm. It is not, however, needed to produce the follower cells that later fuse with these founders. The previous discovery that the founder cells internalize extracellular Jeb⁶ suggested that they express a specific receptor for this secreted protein. And the fact that MAP kinase is activated in these same cells¹ hinted that Jeb could be a binding partner for a receptor tyrosine kinase, as such receptors are known to trigger MAP kinase.

In a different approach, Ruth Palmer's laboratory had been using fruitflies to study the normal function of Alk (although its pathological function in cancer was known, its normal role was not). They showed that Alk is expressed in⁷, and required for the formation of⁸, the early visceral mesoderm in flies.

This was the point at which the two projects intersected: Frasch and colleagues saw the published expression pattern of Alk⁷ and speculated that it could be their predicted receptor tyrosine kinase; Palmer and co-workers saw the similarity of the *jeb* mutants⁶ to their *alk* mutants, and guessed that Jeb could be the binding partner for Alk. They independently used a powerful combination of genetics and biochemistry to show that

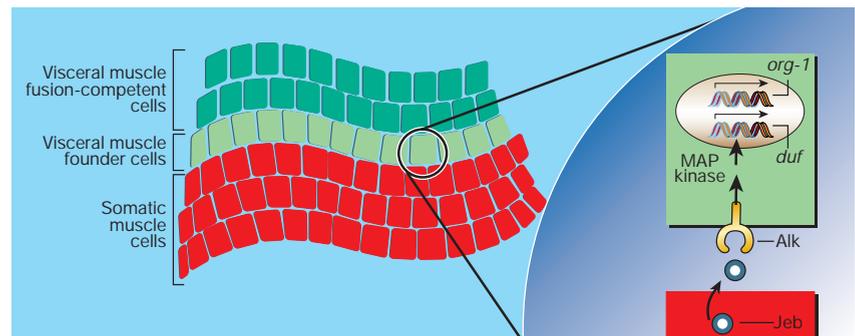


Figure 1 Making muscles in fruitflies. This model is based on the new findings^{1,2}. During the formation of visceral muscles (such as gut muscles), somatic muscles (red) secrete Jeb, while potential visceral founder cells (green) express the receptor Alk. Alk-expressing cells next to Jeb-secreting cells receive the signal, which activates the MAP kinase pathway. This induces expression of *duf* and *org-1*, thus inducing the Alk-expressing cells to become visceral muscle founder cells (pale green).