of lysine-63-linked ubiquitin chains, whereas BRCA1 catalyses formation of lysine-6-linked ubiquitin chains[8] (Fig. 1). Morris *et al.*[4] exploited this difference in ubiquitin-chain linkage to pinpoint the effects of PIAS proteins on BRCA1 activity. They showed that overexpression of BRCA1 increased ubiquitylation events in cells; these events were reduced following PIAS1/4 depletion. Co-localization of lysine-6-linked ubiquitin chains with DSBs was also impaired in BRCA1-, PIAS1- or PIAS4-depleted cells. Furthermore, mutation of the two consensus SUMO-conjugation sites in BRCA1 reduced SUMO1 association and BRCA1-dependent ubiquitylation. Thus, the authors propose that BRCA1 is a SUMO-regulated ubiquitin ligase (Fig. 1).

These findings raise several immediate questions. Are the activities of RNF8, RNF168 and/or other E3 ubiquitin ligases also regulated by SUMOylation? Certainly, such a scenario is possible for RNF8. The current studies[4,5] found that, although recruitment of RNF8 to DSBs was unaffected by PIAS1/4 depletion, RNF8 could not ubiquitylate DSBs, suggesting that it may be inactive in the absence of PIAS1/4. How does SUMOylation stimulate the E3 ubiquitin-ligase activity of BRCA1? Previous studies[9] have shown that DNA damage promotes association between BRCA1 and its E2 conjugating enzyme to form an active E3 ubiquitin ligase. It is therefore tempting to speculate that SUMOylation induces a conformational change in BRCA1 that enhances its binding to an E2 conjugating enzyme. It is clear from the current studies that SUMOylation functions at multiple levels during the DNA-damage response and this will provide fertile ground for future research. The discovery that the SUMO pathway is important for ubiquitylation at DSBs raises the possibility that SUMOylation may activate other ubiquitylation events in the cell. ■

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NANOTECHNOLOGY

Soggy origami

Vincent H. Crespi

Flat microstructures can be designed to spontaneously fold into three-dimensional shapes. Computer simulations of water droplets on sheets of carbon atoms now extend this concept to the nanometre scale.

Explanations of nanometre-scale phenomena often require strange bedfellows of scientific concepts and terminology. The work reported by Patra *et al.*[1] in *Nano Letters* nicely illustrates this trend by marrying chemistry, fluid mechanics, mechanical engineering and physics. The authors have used molecular dynamics simulations to show that the catalytic action of nanodroplets of fluids can cause a simple object — an atomically thin layer of carbon atoms, known as a graphene sheet — to fold spontaneously into complex shapes. The ramifications of this scientific polygamy extend beyond the four fields mentioned above: such spontaneous folding evokes the behaviour of proteins, and graphene sheets also hold promise for electronic applications.

Graphene sheets are single layers of graphite (the familiar stuff in pencils), in which the carbon atoms are arranged in a honeycomb pattern. When Patra *et al.* simulated a small droplet of water sitting on such a sheet, they found that, rather than simply sitting still, the droplet actively deforms the graphene membrane. Because atoms at exposed surfaces in materials are less stable than those buried deeper within, the authors' droplet–membrane system collectively deforms to minimize the number of exposed atoms and hence lower the system's energy. The precise deformation depends on the shape of the graphene sheet and the diameter of the droplet, but, in general, the sheet wraps up around the droplet to form folds, scrolls or troughs (Fig. 1a). When a droplet interacts with a sheet shaped like an open, four-petalled flower, the petals fold up around the droplet to form a closed bulb (Fig. 1b).

In principle, a graphene membrane without a droplet could also lower its energy by bending, so that some of the surface carbon atoms become buried in the interior of a more compact shape. But the transition of an exposed, flat membrane into a smaller, folded package is problematic for an isolated sheet: the energy cost of forming intermediate, partially curled shapes is not compensated for by the short-range attraction between the approaching surfaces until the sheet has bent enough for the surfaces to touch.

This is where the nanodroplets come in. Patra and colleagues' study[1] shows that fluid droplets act as catalysts for graphene deformation — they remove the energy barrier that prevents folding reactions, without themselves undergoing any structural changes. Remarkably, after a droplet has done the work of folding the sheet, it can be expelled from the resulting structure as the opposing graphene surfaces press tightly against each other. Apparently, graphene surfaces prefer being wet to being naked, but they prefer the contact of other graphene surfaces even more. As a result, fluid nanodroplets can cleanly convert flat graphene sheets into folded bilayers, then leave gracefully after their work is done. Such bilayered graphene systems are interesting in their own right as they profoundly alter the remarkable electronic properties of graphene[2].

Spontaneous curling or folding is not unique to soggy graphene. It is also seen in a variety of other systems, ranging from micromachines to biomolecules. The spontaneous deformation of flat sheets was a nuisance in early work on micromachines that were etched from silicon or related materials. When thin sheets of material were released from an underlying substrate, they would curl up in an uncontrolled

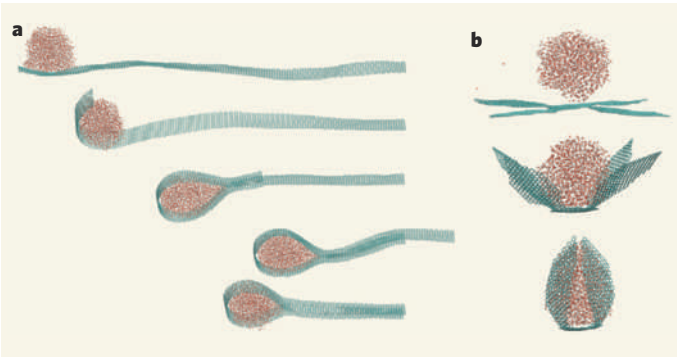


Figure 1 | Folding sheets. Patra and colleagues' molecular dynamics simulations[1] reveal that droplets of water cause atomically thin layers of graphite (graphene sheets) to fold up into more compact shapes. **a,** This simulation shows that a nanodroplet of water molecules (red) causes the free end of a graphene ribbon 30 × 2 nanometres in size to wrap around it. The two opposing sheets then slide along each other, folding the ribbon in half. **b,** Here, a droplet of water causes the 'petals' of a flower-shaped graphene ribbon about 13 nanometres across to fold up around it. (Images taken from ref. 1.)

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fashion to release previously hidden internal stresses in the material, thus destroying the carefully planned geometry of the desired machine.

The unwanted deformations of micromachines were subsequently brought under control, and even turned to good use, by deliberately engineering stresses into materials to generate a preferred direction for bending. This can be achieved by considering the atomic structures of the materials. Every crystalline solid has its own preferred spacing between constituent atoms — the atoms in germanium, for example, are more widely spaced than those in silicon. If two sheets of different crystalline materials are layered to form a thin bilayer sheet in which the atoms across the interface are mutually aligned, then the layer that prefers a larger inter-atomic spacing is placed under compression, whereas the other layer is placed under tension. These internal strains can be relaxed if the sheet spontaneously curls away from the compressed side. Such systems can be designed to bend or curl into desired shapes, such as scrolls, spirals and even pop-up structures[3,4]. By contrast, there is no way to build such stresses into a single layer of graphene. Patra and colleagues' findings[1] circumvent this problem: the interactions of the graphene sheet with the liquid drop define the way that the sheet will curl.

The interactions of fluids with materials have also been exploited at the micrometre scale to create spontaneously folding structures. In these cases, the size of the structures allows the use of photolithography — a finely honed technique best known for sculpting integrated circuits out of silicon — to precisely define the geometry of initially flat shapes, which subsequently fold when regions of solder within them are melted. The natural tendency of the solder droplets is to minimize their exposed surface area; in doing so, they induce the structures to pull themselves into more compact, three-dimensional objects such as cubes or tetrahedra[5]. Patra and colleagues' simulations[1] potentially extend this ingenious technique to objects a hundred-fold smaller.

The three-dimensional structures of polymeric biomolecules, such as proteins and DNA, are formed by similar, exquisitely precise folding of one-dimensional chains. Humans have learned to exploit this phenomenon, particularly in the practice of DNA origami, wherein specific interactions between complementary DNA strands are programmed to interweave a backbone helix into a desired shape through the incorporation of so-called staple strands[6,7]. The folding of proteins, by contrast, is governed at the crudest level by the tendency of hydrophobic (water-repellent) regions to curl up within the interior of folded protein structures. In this way, hydrophobic protein domains become shielded from their watery environment by hydrophilic (water-attracting) regions of the same protein strand. Could hydrophobic or hydrophilic groups be engineered into graphene to modulate its folding, so extending the one-dimensional lessons of biology to the two-dimensional world of graphene? The jury is still out, but Patra and colleagues' preliminary work[1] certainly opens up investigations of this idea.

The quantitative details of Patra and co-workers' empirical simulations — particularly those concerning subtle sheet–fluid and sheet–sheet interfacial interactions — merit verification by more precise methods. For many practical applications, graphene would lie on a substrate, and so it would also be useful to incorporate sheet–substrate interactions into a second generation of simulations. But the fundamental physics described by Patra and colleagues' models is undoubtedly correct. Experimental validation of their findings is the next obvious step. The availability of a wide assortment of fluids suggests that the physical balance of fluid–sheet and fluid–fluid interactions required to bring about graphene origami should be possible in the real world. ■

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NEUROSCIENCE

New tricks and old spines

Noam E. Ziv and Ehud Ahissar

Imaging of brain structures in living mice reveals that learning new tasks leads to persistent remodelling of synaptic structures, with each new skill associated with a small and unique assembly of new synapses.

The notion that structural changes in brain circuitry underlie certain forms of learning is widely accepted, yet this belief has been frustratingly difficult to establish experimentally. Two studies, one by Xu *et al.*[1] (page 915) and one by Yang *et al.*[2] (page 920) published in this issue, provide compelling evidence that learning new motor tasks (and acquiring new sensory experiences) is associated with the formation of new sets of persistent synaptic connections in motor (and sensory) regions of the mouse brain. These findings suggest that synapse assemblies, rather than cell assemblies, might be viewed as the elementary entities (engrams) of stored memories.

At a basic level, the brain can be viewed as a vast network of neurons connected to each other by specialized structures known as synapses. Most synaptic connections are formed between axons (the slender and elongated extensions that carry the signals generated by neurons) and dendrites (highly branched extensions that are specialized for receiving signals originating in other neurons). Most axodendritic synapses are found on dendritic spines, which are tiny protrusions that extend from dendritic shafts in large numbers (Fig. 1a, overleaf).

It has long been assumed that structural changes in this complex circuitry provide the basis for long-term memory formation or the learning of new tasks[3]. The development of new imaging tools[4] over the past decade has opened the door to an experimental evaluation of this assumption as it has allowed for longitudinal studies of axonal and dendritic morphology in the brain of living animals (mainly mice). Somewhat surprisingly, it has become evident that overall neuronal morphology is remarkably stable over long periods (months and beyond). What such studies have revealed, however, is that structural changes do occur at the level of individual synapses, manifested by the appearance of new dendritic spines and the disappearance of others over the course of hours and days[3,5,6]. Interestingly, the extent of spine remodelling can be altered by experimental manipulations, such as depriving the animals of sensory input (from the whiskers or eyes)[3,5,6]. Yet a direct relationship between spine remodelling and learning had yet to be demonstrated.

The two studies in this issue[1,2] provide strong evidence for this link. In both studies, mice were trained to perform a new motor task (reaching for a single seed[1] or remaining on an accelerating rotating rod[2]), and two-photon microscopy[4] of the living animals was used to investigate whether successful training was associated with changes in spine remodelling beyond those observed in untrained mice. Both studies revealed that by the end of the first 1–2 days of training (and as soon as one hour after training[1]), twice as many new spines had appeared in the brain of trained mice compared with untrained mice. Continuous training was subsequently followed by increased rates of spine elimination, and so, after 1–2 weeks,

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