systems for many different types of assay.

Significant issues remain to be addressed. If the CD pick-up head is to be used to detect many different molecules simultaneously, multiple capture molecules will have to be immobilized on surfaces suitable for use with the CD pick-up heads. This is almost sure to require a more flexible technology than the stamping method used by Lange *et al.* Optical alignment issues will also need to be addressed. In Lange and colleagues' study, the CD pick-up head is only one part of the optics: it is combined with a microscope stage for coarse adjustment of the magnification, as well as a lateral translation stage to adjust the position of the line of sight over the substrate. Although it may be possible to use built-in hardware in a commercially available CD player to perform these functions, this has yet to be demonstrated.

One noteworthy advantage of the CD-pick-up approach, alongside small size, low cost and high resolution, is not emphasized by the authors. Although an assay signal has never actually been generated using a CD as a sensing surface, biochemical manipulations have already been performed directly on a CD. Externally readable fluorescence signals have even been generated in channels within the disc[2–5] — the challenge here being the use of centrifugal force to move the fluids through the processing steps on the surface of the CD to the readout position. The combination of such fluidic approaches with *in situ* signal generation as demonstrated by Lange *et al.*[1] could potentially lead to a sea change in medical diagnostics. Imagine in the future buying a 'respiratory pathogen CD' from the local pharmacy when you catch a cold, inserting your self-test swab and placing it in your portable player to find out whether you should take antibiotics or stick to the chicken soup. ■

Frances S. Ligler and Jeffrey S. Erickson are in the Center for Bio/Molecular Science and Engineering, Naval Research Laboratory, Code 6900, Washington DC 20375-5348, USA.
e-mails: fligler@cbmse.nrl.navy.mil; jerickson@cbmse.nrl.navy.mil

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PHYSICAL CHEMISTRY

Stressed molecules break down

Steve Granick and Sung Chul Bae

Tough carbon–carbon bonds can snap in certain large molecules just because the two sides of the molecule cannot agree on which way to go during adsorption. Heresy? The view through the microscope suggests otherwise.

On page 191 of this issue[1], Sheiko and colleagues show that the mechanical deformation induced merely by the adhesion of a complex molecule to a surface can trigger the break-up of that molecule. They thus provide convincing support for the seemingly heretical notion that the commonplace and unremarkable process of adsorption to a surface can bring about what otherwise occurs only with the greatest effort: the rupture of the strong, covalent carbon–carbon bond.

The system designed by the authors[1] is elegant in its simplicity. They placed brush-like, polymeric macromolecules on various solid and liquid surfaces to which the molecules' side-chains (the 'bristles') were strongly attracted. This attraction drove the bristles to spread out so as to maximize their contact with the surface, in turn causing the polymeric backbone of the molecule to stretch until it was eventually strained too far. Direct imaging of the size of the molecules using atomic force microscopy proved that they had been torn apart, just as if the rope had failed in a game of tug of war (Fig. 1).

When a chemical bond snaps, a chemical reaction takes place. But exactly how can a purely mechanical effect have chemical consequences? That is the wider question investigated by a field known as chemomechanics[2]. Future research in this area might well focus on whether mechanical stress shifts the energy level of the transition state of a chemical reaction, through which reactants must pass before becoming products. This view has long been held for 'hard' materials, such as metals, ceramics and semiconductors (steel, for example, corrodes most easily when stressed and bent[3]). Mechanical stress could thus lower the activation threshold of certain reactions, making it easier to kick-start them, or even, depending on the magnitude of the stress applied, switch them off and on.

Organic systems such as that of Sheiko *et al.*[1] add a new twist: whereas the basic unit of hard materials is the atom, that of an organic material is the molecule. The added complexity of a molecule's internal architecture means that the kind of stress transmission described by the authors could not have been observed in an atomic system. In biology, the fact that a mechanical stimulus has chemical consequences — for example, in cellular processes that sense mechanical change[4] or changes in the conformation and function of ion channels in lipid membranes[5] — is being increasingly acknowledged. Thus, investigations of the effect of stress on complex molecules have considerable appeal.

In many organic materials and elastomers (rubbers or rubber-like plastic), the internal architecture of the molecule focuses large stresses on weaker chemical bonds, and stress-induced scission of chemical bonds in such materials is a costly problem[6]. We believe that the work of Sheiko and colleagues[1], by pointing the way towards understanding this ubiquitous and deleterious phenomenon, could provide a general model for designing molecular materials that have an architecture better able to cope with mechanical stress. Such research has myriad technological implications, because the ideas suggested here comprise a new paradigm for solving those problems.

What is in our opinion even more exciting is that there is a general proof-of-concept here — that slow or even forbidden chemical reactions can be activated by mechanical stress. Chemical reactivity clearly depends on the relative orientation of the reactants; so could mechanical deformation be used to place molecules in

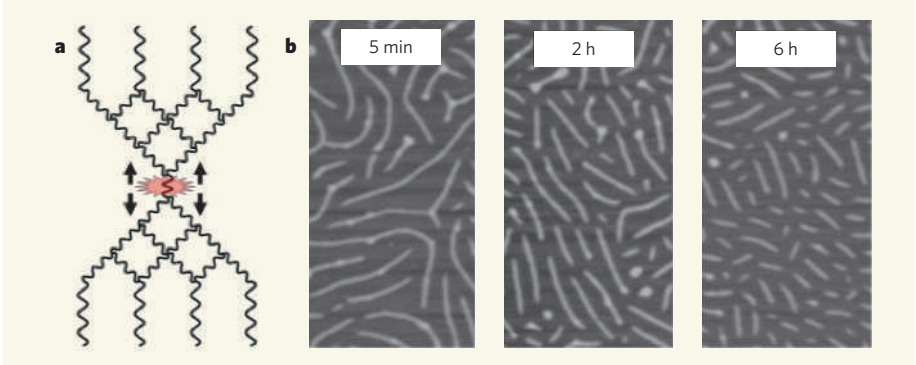

Figure 1 | Bond breaking. a, Channelling mechanical stress to specific, weaker chemical bonds can trigger chemical reactions that otherwise occur only with great effort. **b,** Sheiko *et al.*[1] implemented this idea with brush-like macromolecules on a solid surface. As the bristles of these brushes spread to maximize their contact with the surface, the resultant force is concentrated at the middle, causing chemical bonds to break: the molecules' length thus decreases with time.

a more favourable alignment for reaction? For example, friction and confinement offer a versatile way to align molecules[7], and tribologists, who earn their bread from the study of these things, have known for a long time that friction promotes chemical reactions[8]. The tribological question[7,8] is not directly addressed in Sheiko and colleagues' experiments, but will be an interesting motivation for further work.

And what about using the heat released to accomplish useful chemical change? Carbon–carbon bonds, by dint of their strength, release a lot of energy when they are broken — just as, in a bout of tug of war, energy is lost when the rope fails and competing teams fall to the ground. Although Sheiko *et al.* did not set out to capture energy from breaking carbon–carbon bonds, there is no reason that molecules could not be designed that use this energy for productive chemical means. In this area, too, Sheiko *et al.*[1] have presented a fundamental proof-of-principle on which further efforts can be built and go beyond the more obvious, unwanted consequences of mechanical degradation. ■

Steve Granick and Sung Chul Bae are in the Departments of Materials Science and Engineering, and Chemistry and Physics, University of Illinois, Urbana, Illinois 61801, USA.
e-mails: sgranick@uiuc.edu; sungbae@uiuc.edu

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COMPARATIVE GENOMICS

Difference of expression

Rasmus Nielsen

Evolutionary studies tend to focus on alterations in proteins. But evolutionary change can often occur through modified gene expression, a process that is now under investigation with species-specific microarrays.

Gene expression, the major determining factor of protein abundance in the cell, is regulated by various mechanisms, such as protein binding to the DNA sequence and interference by small RNA molecules. On page 242 of this issue[1], Gilad *et al.* describe their study of gene expression in four primates. Their work is aimed at identifying similarities and differences in gene expression between humans and their nearest relatives.

As we elucidate the complex molecular machinery that controls gene expression, our ignorance of its role in evolution is becoming increasingly alarming. In most cases, we know little about the way in which gene expression is involved in how organisms adapt to new environments or otherwise evolve. It has long been hypothesized that adaptation over short evolutionary time may often proceed by modifications in the regulation and interaction of genes rather than in the protein gene-products themselves[2]. Proteins tend to interact in complex networks, and so small changes in the abundance of one protein may have profound consequences. At the DNA level there may be many different mutations that affect gene-expression levels, but very few potentially beneficial mutations that directly affect protein function. Nonetheless, for convenience, most evolutionary studies have focused on protein evolution, leaving gene expression as one of the great unknowns in evolutionary biology.

Gilad *et al.*[1] make new strides in this field of research. They compare gene-expression data in humans, chimpanzees, orangutans and rhesus monkeys to identify genes that have changed their level of expression in the human lineage. This research differs from earlier studies[3,4] in using microarrays designed specifically for each species. Microarrays consist of a number of probes that bind messenger RNA from specific genes (mRNA is the linking molecule between a gene and the protein it encodes). By determining how much mRNA binds to each probe, the relative abundance of mRNA from each gene can be assessed. However, if the same microarray is used for all species, results may differ between species because of species-specific mutations that affect the binding affinity of the probes. Although this problem can be partially circumvented by removing genes that have such mutations, species-specific microarrays are the only known way to obtain a fair comparison among several divergent species without the loss of any genes.

Using this technology, Gilad and colleagues demonstrate that most genes are under natural selection to maintain a constant level of expression, but that a few genes show evidence of species-specific changes. The fact that selection in most cases is working to maintain expression levels near some optimum is not surprising — levels of expression of a gene that are too high or too low would presumably often be detrimental to an organism. Gilad *et al.* also observe no systematic increase or decrease in the regulation of gene expression in either humans or chimpanzees, contrary to previous claims to this effect[3–5]. But the authors do find that some groups of genes, particularly those encoding gene-transcription factors, tend to include greater numbers of upregulated genes in humans. Transcription factors are proteins that themselves play a role in regulating expression levels. So this observation is further support for the view that many evolutionary changes that are specific to humans may be related to gene expression.

Gilad *et al.*[1] also find that genes that are significantly up- or downregulated in humans, compared with other species, are often genes that have changed rapidly at the DNA-sequence level[6]. So there seems to be a correspondence between genes with altered expression and genes that have been targeted by positive darwinian selection in their protein-coding regions. This makes sense — we would expect changes in the function of a protein to be followed by changes in its distribution and abundance. Likewise, we may expect genes that have suffered a loss or reduction in functionality to subsequently experience an increased rate of evolution in both the sequence of the protein it encodes and its expression level, because selective constraints on it will have been relaxed.

What factors might be causing differences in gene expression between species? Such factors could include changes in the DNA close to the gene, for example changes in transcription-factor binding sites, or in distantly located elements such as gene enhancers, RNA genes or genes encoding transcription factors. Quantifying the relative importance of the evolution of these various elements will not be easy, but large-scale studies comparing many different organisms should reveal correlations between evolutionary changes at the DNA level and changes in expression level or pattern. The comparative analysis of expression data may thereby serve to detect functional correlations between DNA and expression levels in organisms in which it is difficult to carry out direct studies using standard genetic techniques. The result, I predict, will be a new perception of the mechanisms underlying evolutionary change — one in which the emphasis is on changes in regulatory elements, in RNA genes and in segments of DNA other than protein-coding genes. ■

Rasmus Nielsen is at the Institute of Biology and the Centre for Bioinformatics, University of Copenhagen, Universitetsparken 15, 2100 Copenhagen Ø, Denmark.
e-mail: rasmus@binf.ku.dk

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