hypothesized that the external stimulus modified the molecular geometry of the ground state of $(OPV)_5$ and left the excited state essentially unperturbed. The force stretched the molecule by 0.2–0.3 Å, reducing the torsional angle of the backbone and lowering the steric repulsion among the alkyl chains of the molecule. This effect was proportional to the applied force producing linear $\Delta E/\Delta F$ dependence. Similarly, Hinze and co-authors, who studied individual molecules, observed an almost linear shift in the transition energy when the compressive stress on their aromatic chromophore was increased. The absolute value of the slope of the $|\Delta E|/\Delta F$ curve ranges between 0.0025 and 0.02 eV nN^{-1} with a mean of 0.008 eV nN^{-1} (the significant variability of this value is most likely to be caused by the particular geometry of the tip–molecule contact). Both studies show that anisotropic tensile (pulling) and compressive (pushing) stress have comparable energetic effect on the conformational energy of molecules as indicated by their fluorescence properties.

These works point towards a possible exploitation of the sensitivity that individual molecules possess as a function of external forces. To this end, the use of AFM tips to perform chemistry by direct bond scission has already been demonstrated, as a proof-of-principle[5]. Scaffolding structures, DNA origami for instance, could be used to position mechanosensitive molecules in specific places and a chromophore, which is not directly manipulated, could provide an optical read out, to report on the force effects on the overall system. Following this argument, synergetic catalytic centres for cascade reactions could be envisaged. Perhaps in the short term, force-sensitive chromophores could be used as sensors with multiple optical read outs, each corresponding to the emission maxima observed in the work of Hinze and co-workers. A problem that still needs to be overcome, however, is to make the dye's spectral emission shift in a defined direction and then properly calibrate the optical response with the input level. Alternative routes for more robust read outs in this kind of nanoscopic force-sensor application could make use of entropic springs whose extension is monitored by Förster resonance energy transfer for precise distance measurements[6,7]. ❐

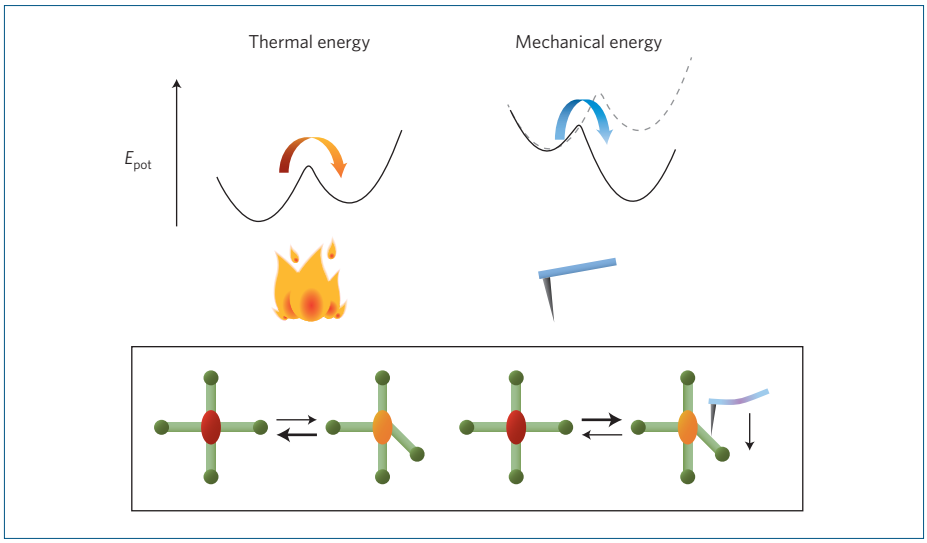

Figure 1 | Schematic of the effect of thermal energy and directional forces on the potential energy (E_{pot}) diagram and transition rates. Both effects increase the number of molecules that cross a reaction barrier, but the working principle is different. Thermal energy does not lower the barrier but increases the internal molecular energy of the molecules, which facilitates barrier crossing. In contrast, forces change directly the barriers and local minima in the potential energy landscapes (dashed line, E_{pot} without force; black line, E_{pot} modified by force). In the box we compare the effects of thermal and mechanical energy on the multichromophore fluorescent molecule TDI-4PDI with one central TDI unit (red/orange ellipse) and four peripheral PDI units (green spheres). The fluorescence of TDI is spectrally different for distinct conformers. As depicted in the potential energy landscape above, the reaction equilibrium can be strongly shifted (black arrows) by force, which is not easily possible by thermal energy.

Claus A. M. Seidel and Ralf Kühnemuth are at the Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1 Geb. 26.32.02, 40225 Düsseldorf, Germany.
e-mail: cseidel@hhu.de

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NANOMECHANICAL SENSORS

Measuring a response in blood

Nanomechanical cantilevers can determine the concentration of active drugs in human serum.

F. Huber, H. P. Lang and Ch. Gerber

The recent increase in the number of bacteria that are resistant to drugs, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), represents a significant threat to public health. According to a report by the Centers for Disease Control and Prevention[1], for example, 2 million people are infected and 23,000 die each year in the US from bacteria that are resistant to antibiotics; many more deaths occur as the result of complications associated with other conditions caused by an antibiotic-resistant infection. This increase in drug-resistant bacteria combined with a decline in the development of antibiotics, means that drug resistance is an impelling global concern[2]. One innovative way to try to address these clinical problems and develop effective therapies is to use mechanical signals, rather than chemical or

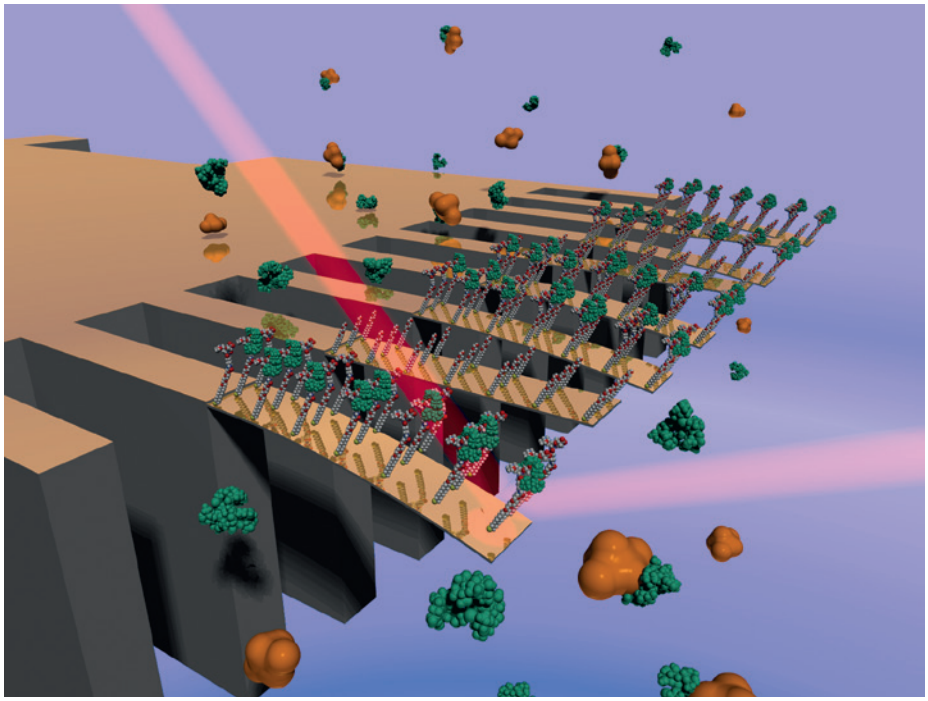

Figure 1 | Working principle of nanomechanical microcantilevers. The gold-coated surface of some of the cantilevers is functionalized with receptor model molecules of lysine-D-alanine-D-alanine (for example, the first cantilever from the left)[4], whereas the other cantilevers are functionalized with the reference molecule triethylene glycol (for example, the second from left), which does not allow binding of the ligand. Antibiotic molecules are depicted in green, floating freely in solution and bound to the receptor molecules. The cantilevers bend in response to the antibiotic molecules binding to the receptor molecules, and the bending is analysed using a laser beam (shown in bright red, deflecting from the first cantilever) and a position-sensitive detector (not shown). Cantilevers are measured sequentially. Image courtesy of Natascha Kappeler and Rachel A. McKendry.

electrical signals, to explore novel antibiotic therapies. Nanomechanical sensors based on microcantilevers provide a technology platform for label-free and sensitive detection of biomolecular interactions[3] on a solid surface. However, the development of a new drug requires a detailed understanding of its therapeutic effects in a complex environment, such as in a patient's blood. Writing in *Nature Nanotechnology*, Joseph Ndieyira, Rachel McKendry and colleagues now show that arrays of nanomechanical cantilevers can characterize the mechanical response of the bacterial cell wall to antibiotics while taking into account their binding to other molecules in solutions that reduce their potency[4].

Nanomechanical sensors work by measuring the bending of a cantilever that is generated by molecular binding/adsorption taking place on the surface of the cantilever (Fig. 1). The bending is a result of surface stress created due to factors such as electrostatic and van der Waals forces, as well as conformational changes of molecules and molecular layers upon a binding event. The main advantage of the microcantilever technique is the possibility to measure forces at the nanoscale, and the versatility of cantilever sensors in life science applications has been previously demonstrated through the detection of RNA[5], proteins[6] and microorganisms[7]. Spurious effects, such as nonspecific interactions and thermal drift, are cancelled out by calculating the differential response of a probe and a reference cantilever.

The researchers — who are based at University College London, Jomo Kenyatta University of Agriculture and Technology, the University of Queensland and the University of Cambridge — investigate the interactions of drug molecules that are in solution with strongly and weakly interfering ligands such as the proteins in human serum[4]. Some of these components of blood can influence the activity of drugs by binding antibiotics and thereby lowering the concentration of the active ingredient. Therefore, the interactions between the drug and competing ligands affect the dosage needed for effective treatment, and an in-depth understanding of these processes is essential for evaluating the effectiveness of antibiotics, as well as for therapeutic drug monitoring. Furthermore, the researchers find that the additional presence of analogous bacterial targets in solution enhances the surface binding activity of antibiotics such as vancomycin. This could boost the efficiency of drugs in killing bacteria. The method could therefore also be used to evaluate new drugs and investigate resistance to antibiotics.

Ndieyira and colleagues use nanomechanical cantilever arrays to explore the mechanisms of antibiotic interactions with the bacterial cell wall and the blood/serum constituents at the same time. The binding of an antibiotic in solution to bacterial cell wall components causes surface stress changes, which illustrates the importance of nanomechanics in antimicrobial action on bacterial cells[8]. Surface receptors on the cantilevers also probe the impact of blood serum on the activity of antibiotics, allowing the correct dosage for a patient to be determined. For each antibiotic drug that is developed, the influence of serum albumin and other proteins must be investigated to evaluate its effect. The nanomechanical technique allows antibiotic activity to be analysed quickly and could therefore help refine dosage prescriptions.

This nanomechanical technology has a number of advantages over methods such as radioactive or fluorescence labelling in immunoassays, quartz crystal microbalance[9] and surface plasmon resonance[10]. These advantages include label-free detection of ligands in solution, and screening of multiple receptor–ligand interactions in parallel and under identical conditions. Ndieyira and colleagues show that methods such as surface plasmon resonance are two orders of magnitude less sensitive compared with the cantilever approach in detecting antibiotics in solution. Importantly, the researchers demonstrate that distinct changes of surface mechanics are drug-specific, and that competing ligands in solution play a fundamental role in modulating these mechanical properties. Moreover, they developed a conceptual framework that allows quantitative judgments in understanding the mode of action of antibiotics in a complex environment to be made.

The direct nanomechanical quantification of an effective dose in clinical studies could help in the development of personalized healthcare. Additionally, the technique could be used to design optimized treatments, particularly in combinational therapy, where it could act as a platform for the early detection of infectious diseases and monitoring of treatments for multidrug-resistant pathogens. The work of Ndieyira and colleagues is also an important step towards fully understanding the role of chemistry and

mechanics in membrane-bound receptor and protein assays.

F. Huber, H. P. Lang and Ch. Gerber are at the Swiss Nano Institute, University of Basel, Klingelbergstrasse 82, 4056 Basel, Switzerland.
e-mail: christoph.gerber@unibas.ch

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QUANTUM COMPUTING

Three of diamonds

Quantum computers require error correction protocols to repair the state of the quantum bits. This has now been demonstrated using a 'majority voting' protocol among a cluster of three defect spins in diamond.

John J. L. Morton and Jeroen Elzerman

From DNA replication to satellite communication, identifying and fixing errors is an essential part of building robust large-scale systems. Common approaches to error correction make use of redundancy (encoding copies of information across more than one entity) and rely on the fact that multiple errors are less likely to occur than a single error. For error correction in quantum information processors, such redundancy requires control over at least three coupled quantum bits (qubits), which is challenging in many systems. Now Gerald Waldherr and co-workers writing in *Nature* and Ronald Hanson and co-workers writing in *Nature Nanotechnology*, report the use of the spins of defects in diamond along with trace nuclear spins in the host lattice to demonstrate the control required to implement a quantum error correction protocol[1,2].

Qubits are extremely sensitive to disturbances from their environment, often leading to quantum information lifetimes in the millisecond range, or less. To make matters worse, performing a measurement on a qubit destroys the information it represents, ruling out error-handling approaches such as continuously measuring and re-setting the qubit (as happens when dynamic random access memory is refreshed). Practical quantum computing therefore only became a real prospect with the advent of quantum error correction protocols[3,4], which map the quantum state of a 'data' qubit across two further qubits, known as ancillae. Using a procedure analogous to majority voting among the three qubits (Fig. 1), it is possible to correct errors in the data qubit without ever measuring its state, thus leaving the quantum information intact. The errors are effectively filtered off into the ancilla qubits, which are periodically reset.

Nitrogen–vacancy (NV) defect centres in diamond (Fig. 2) are among the most promising systems being investigated as potential qubits. They possess an electronic spin whose state can be initialized and read out optically, even at room temperature[5]. This electron spin interacts strongly with the nuclear spin of the defect's nitrogen atom (^{14}N); however, to find the three or more spin qubits requisite for quantum error correction, one has to look to the

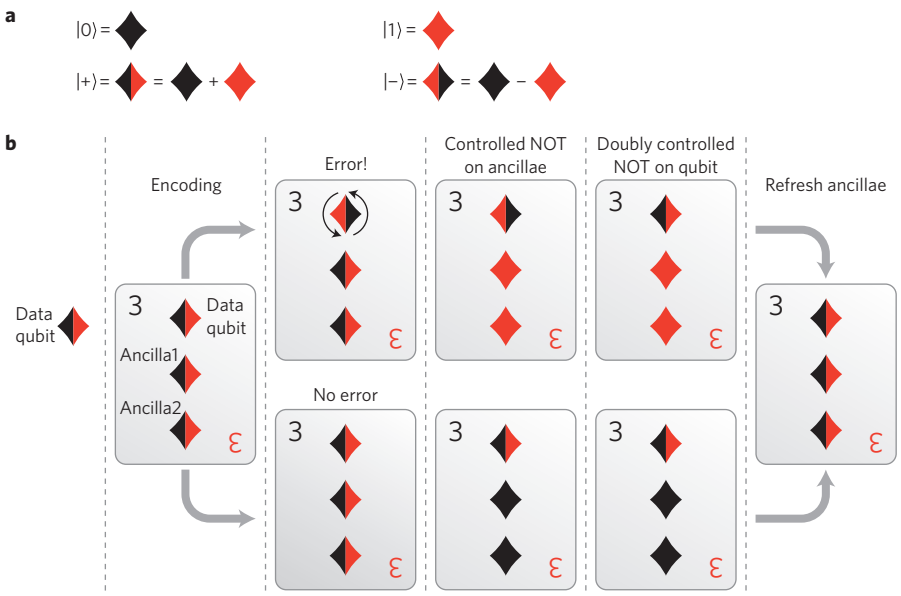

Figure 1 | Schematic representation of a simple three-qubit quantum error correction protocol. **a**, The two qubit basis states $|0\rangle$ and $|1\rangle$ are denoted as a black and red diamond, respectively. The two qubit superposition states denoted $|+\rangle$ and $|-\rangle$ differ only in the phase between the two parts of the superposition. **b**, The error correction protocol is started by encoding the state of a single data qubit onto two additional 'ancilla' qubits. A single phase-flip error can occur on any of the three qubits, changing its state from $|+\rangle$ to $|-\rangle$, but it will most likely leave the other two unaffected (provided errors are uncorrelated and rare). To correct an error on the data qubit, a controlled-NOT operation is performed on the two ancillae, which changes their state from $|0\rangle$ to $|1\rangle$ or vice versa if the data qubit is in state $|1\rangle$. Then a doubly controlled NOT operation is carried out on the data qubit, which changes its state from $|0\rangle$ to $|1\rangle$ if both ancillae are in state $|1\rangle$. This procedure automatically corrects the phase error in the data qubit without performing any error detection measurement. After the ancillae are refreshed to their initial states, the protocol can be repeated.