But what triggers E1 transition between the open and closed conformations? A critical determinant might be an inability of the closed conformation to bind to ATP. Indeed, in the adenylation reaction, ATP binding to E1 precedes its binding to Ubl protein. Furthermore, the E1–SUMO~AMSN structure indicates that, after the adenylation reaction and the release of pyrophosphate, the contacts of the adenylation active site to the ATP phosphates constituting pyrophosphate would be lost. Thus, formation of SUMO~AMP seems to favour stabilization of the E1's closed state. Nonetheless, as dramatic structural remodelling was not observed for E1–SUMO~AMSN, which is in the open conformation[6], the question arises as to whether factors other than Ubl adenylation trigger the conformational change. It could also be that resolving subtle differences between SUMO~AMSN and the natural SUMO~AMP may be necessary to fully reproduce the catalytic details responsible for the conformational change to the 'closed' state.

Olsen and colleagues' structures[6] might also provide clues to understanding the last reaction catalysed by E1 — transfer of the Ubl C terminus from the E1 catalytic cysteine to that of the E2 enzyme. A previous structure[9] showed striking reorientation of a different part of E1 (an E2-binding domain), allowing the E1 and E2 catalytic cysteines to face each other while a gap remained between them. The distinct conformational changes Olsen *et al.* describe raise the question as to whether the E1, the E2, or both enzymes might adopt some other structures for Ubl-protein transfer. The two strikingly different structures of SUMO E1 also raise a more general question. Is dramatic structural remodelling[6] unique to E1, or do other proteins also undergo similar overt structural transformations that we have yet to detect? ■

Brenda A. Schulman is at the Howard Hughes Medical Institute, Department of Structural Biology, St Jude Children's Research Hospital, Memphis, Tennessee 38105, USA. Arthur L. Haas is in the Department of Biochemistry and Molecular Biology, Louisiana State University School of Medicine, New Orleans, Louisiana 70112, USA.
e-mails: brenda.schulman@stjude.org; ahaas@lsuhsc.edu

1. Haas, A. L. & Rose, I. A. *J. Biol. Chem.* **257,** 10329–10337 (1982).
2. Haas, A. L., Warms, J. V., Hershko, A. & Rose, I. A. *J. Biol. Chem.* **257,** 2543–2548 (1982).
3. Hershko, A., Heller, H., Elias, S. & Ciechanover, A. *J. Biol. Chem.* **258,** 8206–8214 (1983).
4. Wilkinson, K. D. *et al. Biochemistry* **29,** 7373–7380 (1990).
5. Pickart, C. M., Kasperek, E. M., Beal, R. & Kim, A. *J. Biol. Chem.* **269,** 7115–7123 (1994).
6. Olsen, S. K., Capili, A. D., Lu, X., Tan, D. S. & Lima, C. D. *Nature* **463,** 906–912 (2010).
7. Walden, H., Podgorski, M. S. & Schulman, B. A. *Nature* **422,** 330–334 (2003).
8. Lois, L. M. & Lima, C. D. *EMBO J.* **24,** 439–451 (2005).
9. Huang, D. T. *et al. Nature* **445,** 394–398 (2007).
10. Lee, I. & Schindelin, H. *Cell* **134,** 268–278 (2008).

QUANTUM MEASUREMENT

A light touch

Aephraim M. Steinberg

A technique used primarily to study fundamental issues in quantum mechanics has now been shown to have promise as a powerful practical tool for making ultra-precise measurements.

'Weak measurement', a technique invented by Aharonov and co-workers[1] about 20 years ago, is a way of probing a quantum system so gently that the famous measurement disturbance guaranteed by Heisenberg's uncertainty principle becomes negligible. Its discovery opened the door for investigation of all manner of quantum phenomena previously deemed inaccessible. The method's downside — that when you probe a system weakly, you acquire little information — seemed a small price to pay for such a qualitative change in the rules of the game. Until recently, such a sacrifice seemed wise only for studying the foundations of physics. But writing in *Physical Review A*, Howell and colleagues[2] show that a clever application of this technique can vastly improve the signal-to-noise ratio of a measurement as simple as the angular deflection of a light beam.

All measurement begins with an interaction between the system under consideration and a measuring device. For instance, the fuel in a car's tank pushes up a float, and it is the position of this float that is sensed. Famously, quantum mechanics teaches us that measurement is a two-way street: any such interaction must also disturb the system being measured. It is as though each time one looked at a car's fuel gauge, the car's fuel efficiency changed randomly, making it impossible to foresee how much longer it could go without refilling.

Weak measurement attempts to circumvent measurement disturbance by greatly reducing the strength of the interaction between the system and the measuring device — to the extent that the response of the measuring device is less than its own quantum uncertainty. This may seem foolhardy; the measurement is made so uncertain (imagine trying to read a fuel gauge whose needle moved only a millimetre when the tank filled up) that an experimenter obtains essentially no information from any individual trial. The solution, well known to any scientist, is to repeat the experiment millions — or even billions — of times, until sufficient statistical significance of the measurement is ensured.

The most interesting features of weak measurement arise when it is conditional, involving preselection and postselection of the state of the quantum system being investigated. Aharonov and colleagues[1] predicted that if postselection has a very low probability (that is, if one conditions the measurement on finding the system in a very unlikely final state) the measurement outcome can be unexpectedly large — larger than any 'legal' value for the property being measured. To stretch an already overextended metaphor, it's as though the gauge for your 50-litre petrol tank occasionally marked 'approximately 1,000 litres of petrol left'. This might seem like nonsense, but theory ascribes real physical significance to such 'weak values'. Because a weak measurement is highly uncertain, on no individual occasion can you conclude that there really are 1,000 litres of petrol left. However, if you repeat the experiment often enough, the mean value turns out to be really that extreme — but only if the postselected state is highly unlikely.

The first experimental realization of a measurement of a weak value was performed by Hulet and colleagues[3], three years after Aharonov *et al.* made their prediction[1]. Since then, weak measurements have been used to study a range of fundamental issues in quantum physics[4–9]. From early on, several workers speculated that the existence of anomalously large measurement results might make weak measurement a practical tool, 'amplifying' otherwise-hard-to-measure effects into the realm of observability. But it was not immediately clear whether the benefit of the amplification would outweigh the cost of a low-probability postselection. This began to change when Hosten and Kwiat used weak measurement to perform the first observation[10] of the spin Hall effect for photonic (as opposed to electronic) systems. They measured the polarization-dependent spatial shift of light beams on refraction through an air–glass interface with a sensitivity on the order of the size of a single hydrogen atom. Dixon *et al.*[11] followed suit and measured the angular deflection of a light beam with the precision of literally a hair's breadth at the distance of the Moon.

It should be noted, however, that in these experiments the object of the weak measurement is not the (very small) unknown quantity one seeks to determine but a known parameter carefully controlled to have a large weak value. The unknown quantity is used as a coupling strength to measure the known parameter, so that even if it is very small, the large weak value makes the final effect observable, allowing us to infer the unknown's value. Controversy remains over to what extent, and under what circumstances, this strategy will offer advantages over traditional measurement techniques.

In their experiment, Howell and colleagues[2] have carried out the first careful accounting of the signal-to-noise ratio attainable in weak

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measurements[2,11]. They demonstrated that, under the right conditions, the ratio may be improved by a factor of 50 or more over standard measurements. Two factors determined their success. First, following Hosten and Kwiat's work[10], they took advantage of another odd property of weak measurements — that the measurement outcomes can be imaginary numbers. This may sound arcane, but the physical implication is simple and striking: instead of merely shifting the position of the needle on a gauge, such a measurement shifts its velocity. Second, they observed that, in practice, measurements of small effects are often dominated by technical rather than purely statistical noise — that is, by the imperfect nature of the measuring device. In these circumstances, the authors find that although the weak measurement amplifies the desired signal, the low likelihood of the postselection succeeding simultaneously reduces the technical noise. These two factors combine to make much smaller effects observable.

It is interesting to note that, although Howell and colleagues' experiment[2,11] could be understood as a sophisticated but entirely classical optical interferometer, it was only invented thanks to the application of some of the newest ideas in quantum-measurement theory. The surprising effects of weak measurement arise from interference, which is at the heart of many high-resolution measurement devices, ranging from atomic clocks to phase-contrast microscopes. Therefore, this brainchild of quantum metaphysics may find its way into yet more practical applications. ■

Aephraim M. Steinberg is in the Centre for Quantum Information and Quantum Control, and the Department of Physics, University of Toronto, Toronto, Ontario M5S 1A7, Canada.
e-mail: steinberg@physics.utoronto.ca

1. Aharonov, Y., Albert, D. Z. & Vaidman, L. *Phys. Rev. Lett.* **60,** 1351–1354 (1988).
2. Starling, D. J., Dixon, P. B., Jordan, A. N. & Howell, J. C. *Phys. Rev. A* **80,** 041803(R) (2009).
3. Ritchie, N. W. M., Story, J. G. & Hulet, R. G. *Phys. Rev. Lett.* **66,** 1107–1110 (1991).
4. Aharonov, Y., Botero, A., Popescu, S., Reznik, B. & Tollaksen, J. *Phys. Lett. A* **301,** 130–138 (2002).
5. Mir, R. *et al. New J. Phys.* **9,** 287 (2007).
6. Lundeen, J. S. & Steinberg, A. M. *Phys. Rev. Lett.* **102,** 020404 (2009).
7. Yokota, K., Yamamoto, T., Koashi, M. & Imoto, N. *New J. Phys.* **11,** 033011 (2009).
8. Steinberg, A. M. *Phys. Rev. Lett.* **74,** 2405–2409 (1995).
9. Smith, G. A., Chaudhury, S., Silberfarb, A., Deutsch, I. H. & Jessen, P. S. *Phys. Rev. Lett.* **93,** 163602 (2004).
10. Hosten, O. & Kwiat, P. *Science* **319,** 787–790 (2008).
11. Dixon, P. B., Starling, D. J., Jordan, A. N. & Howell, J. C. *Phys. Rev. Lett.* **102,** 173601 (2009).

GENETICS

Random expression goes binary

Adrian Streit and Ralf J. Sommer

The production of intestinal cells in a worm embryo is regulated by a network of transcription factors. Studies of these networks in mutant worms provide evidence for stochastic effects in gene expression.

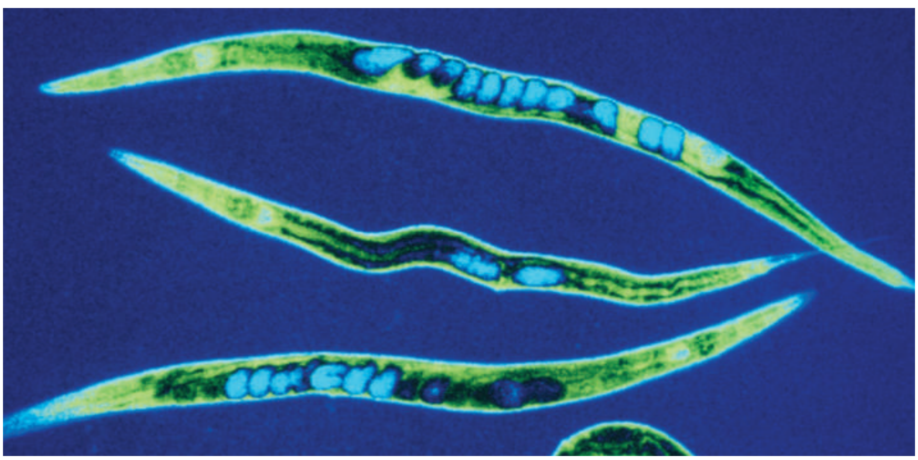
Identical twins are not truly identical. Although to strangers they look very much alike, relatives and friends usually have no problem telling them apart, even from a distance, and they have their own personalities. It is also known that not all carriers of mutations that cause genetic disorders develop the associated disease. Similarly, there are many cases in which only a fraction of a population of organisms that harbours a mutation at a particular genetic locus develops the corresponding mutant characteristics (phenotypes); the rest are of wild-type appearance. This phenomenon, known as incomplete penetrance, indicates the existence of a mechanism that generates diversity even among genetically identical individuals.

Such variability can often be explained by differences in genetic background in non-identical organisms, or by the exposure of individuals to different environmental conditions. But incomplete penetrance is also observed in genetically identical populations of laboratory animals, which are kept under controlled, stable conditions. It has therefore long been assumed that the phenomenon is partly caused by stochastic events, in particular random fluctuations in gene expression, which must reach some threshold level to cause an outcome[1]. That would explain the binary, 'on–off' nature of the effect. But convincing, experimentally validated examples of a stochastic process are scarce.

On page 913 of this issue, Raj *et al.*[2] provide just such evidence. They report that the incomplete penetrance of mutations in the gene *skn-1,* which induces the differentiation of intestinal cells in the nematode *Caenorhabditis elegans* (Fig. 1), can be explained if the randomly fluctuating expression of a downstream gene, *end-1*, must reach a certain threshold to exert its effect.

The model organism *C. elegans* is particularly well suited for analysing mutant phenotypes, incomplete penetrance and related phenomena because it can be kept in the laboratory as genetically identical lines. The organism's invariant cell lineage offers additional advantages for the molecular analysis of gene expression at single-cell resolution. For example, the intestine of *C. elegans* is formed from 20 cells, all of which are descendants of the E cell, which is a great-grand-daughter cell of the fertilized egg and gives rise to intestinal tissue only[3].

The intestinal fate of the E cell's descendants is controlled by a system of transcription factors that represents one of the simplest regulatory networks in worms, thus providing an ideal test case for studying fluctuations in gene expression. The mother provides the worm embryo with two of these factors, POP-1 and SKN-1, which activate transcription of the genes *med-1*, *med-2*, *end-3* and *end-1* (Fig. 2, overleaf), all of which encode transcription factors belonging to the GATA family. The latter two factors in turn activate *elt-2*, which encodes yet another GATA-type factor. The *elt-2* gene is expressed only in the intestine, and controls the expression of a large number of genes involved in intestinal differentiation. It also activates itself through a feedback loop, to ensure its continuous expression. The different components of this regulatory network show a high degree of interconnectivity and



J. KING-HOLMES/SPL

Figure 1 | An organism with guts. The intestine of the nematode worm *Caenorhabditis elegans* was used as a model system in Raj and colleagues' genetic study[2] of the phenomenon of incomplete penetrance.

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