

measurements<sup>2,11</sup>. 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<sup>10</sup>, 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<sup>2,11</sup> 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. ■

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## 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<sup>1</sup>. That would explain the binary, 'on-off' nature of the effect. But convincing, experimentally validated examples of a stochastic process are scarce.

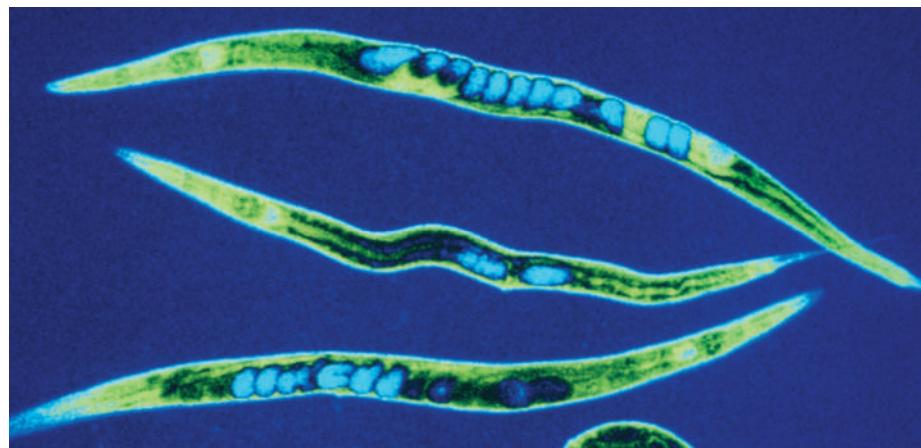
On page 913 of this issue, Raj *et al.*<sup>2</sup> provide

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<sup>3</sup>.

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



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**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<sup>2</sup> of the phenomenon of incomplete penetrance.

**50 YEARS AGO**

A further Committee of the Commonwealth Education Conference considered the extent to which the countries of the Commonwealth could help each other to meet their needs for training teachers ... Already more than 2,500 teachers a year leave the United Kingdom for service in other Commonwealth countries and the Government is to make every effort to increase this number. Canada, Australia and New Zealand made definite offers of assistance at the Conference, and both India and Pakistan hope to encourage their teachers to serve in other Commonwealth countries ... Steps should also be taken to promote a climate of opinion which will recognise service abroad as a professional asset.

From *Nature* 20 February 1960.

**100 YEARS AGO**

The first part of a general description of the engineering and constructional features of the Panama Canal appears in *Engineering* for February 11 ... An average of 1,000,000 lb. of dynamite per month is consumed for the entire work, and the number of accidents has been relatively small, although, owing to the number of men in contracted areas, the casualties have been great. Premature explosions, attributable to concussion during loading, led to the substitution of pine-rammers for those of lignum vitae ... No holes are now loaded which cannot be fired the same day, a precaution necessitated by the premature explosion of 22 tons of 45 per cent. dynamite at Bas Obispo, probably owing to some of the nitroglycerine having been liberated and exploded by concussion by a dobie shot in the vicinity. Accidents have occurred during electric storms, and the only possible precaution is now taken by stopping work.

From *Nature* 17 February 1910.

**50 & 100 YEARS AGO**

redundancy (for example, *end-1* and *end-3* perform essentially the same function: activating *elt-2*), which ensures that wild-type embryos show no variability in their phenotype<sup>4</sup>.

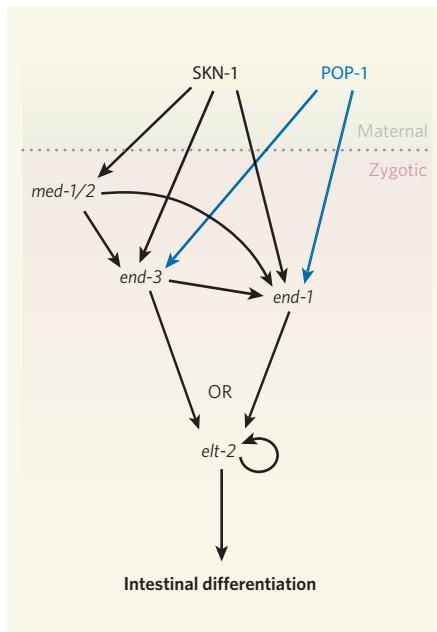
To study random fluctuations in gene expression in this regulatory network, Raj *et al.*<sup>2</sup> used a fluorescence-based technique that detects single messenger RNA molecules in cells<sup>5</sup>. They were thus able to count the absolute numbers of mRNA molecules for *med-1*, *med-2*, *end-1*, *end-3* and *elt-2* in wild-type embryos and in embryos that had mutant versions of *skn-1*. It is known that *skn-1* mutants show an incompletely penetrant failure to induce intestine (they die late in the embryo's development, with most, but not all, embryos lacking intestinal cells). The authors observed that *skn-1* mutant embryos essentially fail to express *med-1/2* and *end-3*, whereas the expression of *end-1* was highly variable, ranging continuously from zero to almost wild-type levels.

Interestingly, Raj *et al.* found that *elt-2* — which in the absence of *end-3* was now controlled by *end-1* alone — did not follow this continuous pattern, but seemed to be activated in a bimodal manner. In other words, in any particular cell, *elt-2* mRNA either was absent or was present at almost wild-type levels. This suggests that when *end-1* mRNA molecules reach a threshold level, the *elt-2* auto-activating feedback loop is initiated, leading to near wild-type-level expression of *elt-2* and intestinal differentiation of the corresponding cell. If the *end-1* threshold is not reached, then *elt-2* expression collapses and intestinal differentiation fails.

To test this hypothesis, the authors counted *end-1* and *elt-2* mRNAs simultaneously in mutant embryos. Sure enough, none of the embryos that had low *end-1* mRNA levels expressed *elt-2*. But in *elt-2*-expressing cells, the authors found clear indications that *elt-2* is expressed once a threshold level of *end-1* expression has been reached, rather than observing a linear relationship between the numbers of *elt-2* and *end-1* mRNAs. It remains to be seen how the absence of *skn-1* function leads to the observed variability; additional techniques will need to be used to pinpoint the exact mechanism.

Raj and colleagues' findings<sup>2</sup> indicate how stochastic, continuous variation in gene expression can lead to a bimodal output and to the incomplete penetrance of a mutant phenotype. The simple regulatory network that controls the differentiation of intestinal cells in *C. elegans* also illustrates that such stochastic events can be buffered through connectivity and redundancy to ensure that essential developmental processes are protected. Redundancy, although long known to geneticists, has always been hard to study experimentally. The single-molecule technique used by Raj *et al.* opens up new opportunities for studying this phenomenon at the molecular level.

So, what might all this mean for identical twins? Non-essential regulatory processes might often be less robust than the system



**Figure 2 | Control of intestinal differentiation in the embryos of *Caenorhabditis elegans*.** The intestinal cells of *C. elegans* are derived from the E cell (not shown), a great-grand-daughter cell of the fertilized egg (the zygote). A network of genes and transcription factors ensures that the E cell's descendants turn into intestinal tissue only. The factors POP-1 and SKN-1 in the worm embryo are provided by the mother. POP-1 activates the genes *end-1* and *end-3*; SKN-1 also activates *med-1* and *med-2*, which in turn activate *end-1* and *end-3*. The *end-1* and *end-3* genes encode transcription factors that activate *elt-2*, a gene that controls intestinal differentiation and also activates itself to ensure its continuous expression. Mutant embryos in which SKN-1 activity is abolished die, with most, but not all, of these embryos lacking intestinal cells. Raj *et al.*<sup>2</sup> report that this indeterminate differentiation is controlled by variability in the expression of *end-1*.

investigated in the present study<sup>2</sup>. Mechanisms that are closely similar to the one that leads to incomplete penetrance of *skn-1* mutations are therefore likely to contribute to the generation of random phenotypic differences among genetically identical individuals. Further investigations are needed to confirm this, and to address other questions of incomplete penetrance.

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