50 & 100 YEARS AGO

50 YEARS AGO

The most important tercentenary of the year is undoubtedly that of the birth of Edmond Halley, the gifted mathematician, astronomer and pioneer meteorologist... In 1686 he made his famous visit to Newton at Cambridge which led the latter to prepare the "Principia". In 1686, after the first part had been delivered to the Royal Society, Halley not only undertook to supervise the printing, but also made himself responsible for the entire cost. This was because the finances of the Royal Society were so low that it was not only unable to carry out its original resolution to pay for printing the "Principia", but was even unable to pay Halley, then assistant secretary, his promised stipend of £50 a year. In July 1687, in the same month that Halley sent Newton twenty copies of the "Principia" to "bestow on your friends in the University", he accepted seventy copies of Willughby's "De Historia Piscium", published the previous year by the Royal Society, in lieu of some eighteen months salary.
From *Nature* 7 January 1956.

100 YEARS AGO

The mounted skeleton of *Triceratops prorsus*...is interesting as displaying another Dinosaur of a distinct and very remarkable type. Triceratops was a quadrupedal reptile of quite moderate size, the skeleton...being not more than 25 feet in length and 10 feet in height... Two powerful horn-cores of the bovine type, 25 feet in length, rise from the frontal bones of the skull, at the base of which are the round bony orbits. The snout is narrow and pointed, and carries a third smaller horn upon the nasal bone. Behind the pair of frontal horns is an immense frill of bone spreading back over the occipital region and covering the first six vertebrae; it was 2 feet 6 inches long and 3 feet broad, resembling an immense Elizabethan ruff, ornamented with about twenty-four pointed bosses of bone along its border.
From *Nature* 4 January 1906.

synchronized[2]. Zhou *et al.*[1] analyse a simpler negative-feedback model, changing the natural autoinducer into an autoinhibitor that acts with some time delay. The system did not oscillate; instead, the level of autoinhibitor remained at a single steady state. But when enough random noise was added, stable and synchronized oscillations appeared.

How can this happen? Picture a mobile hanging from a baby's stroller. Although each pendulum of the mobile can swing back and forth periodically, none will actually move until a force is applied. The system is, however, poised to oscillate, and even a few petulant hits or a gust of wind can act as a trigger. If all the pendulums are affected at the same time and in the same way (in our analogy, if there is correlated extracellular noise), they can oscillate together. If the pendulums are connected by a string (if the cells can communicate), this is even easier to achieve: any pendulum that is out of synchrony is then literally pulled into phase by the others.

The analogy is not perfect: the combination of negative feedback and time delays can, under certain conditions, cause oscillations even without any external forces. And noise affects these conditions: even uncorrelated fluctuations can change the average concentration at which cell decisions are made, turn discrete all-or-nothing switches into smooth, continuous responses, or even sharpen continuous responses into discrete switches[3]. Uncorrelated noise could thus, in principle, sufficiently change the characteristics of a non-oscillating feedback system to produce stable oscillations[3,4].

This goes against our expectation that noise blunts a signal. In fact, the combination of noise and nonlinear kinetics is capable of almost anything, even in the simplest systems. To take an example from biochemistry, the rate at which two identical protein monomers dimerize to form an active enzyme depends on the square of the monomer concentration. Cells with higher than average monomer levels thus contribute disproportionately to the average rate of dimerization in the population. If each cell had exactly one monomer, no enzyme would be produced. But if fluctuations were such that half of the cells had two monomers and the other half none, some enzyme would be made even though the average amount of monomer is the same[5]. Because protein fluctuations in turn respond very differently to the rates at which the genes encoding them are transcribed and translated[6], changing both rates simultaneously can have unexpected effects on the average rate of enzyme production, potentially even making it proportional to the cube, rather than the square, of the average monomer concentration.

Correlated fluctuations between different components in the same cell can be even more useful. Studies using two identically regulated alleles (gene variants) that encode fluorescent 'reporter' proteins show that some protein noise is correlated and shared between alleles, but that other sources of protein noise are uncorrelated and experienced separately[7]. From the viewpoint of each gene individually, there is little difference between the two types of noise; crucially, however, shared noise can be used to coordinate action between them. To continue the biochemical example, consider this time two different types of monomer that combine to form an active enzyme complex: if the noise in the expression of the two monomers were correlated, randomly pushing up both concentrations at the same time, cells could form enzyme complexes more efficiently.

Zhou and colleagues' work[1] is just one example of the growing body of research that shows how cells can use noise to suppress other noise, or to create oscillations, multi-stabilities and many other coherent kinetic traits. Coupled with the recognition that even simple, noise-free mechanisms can generate 'deterministic chaos' — acting to amplify infinitesimal environmental perturbations into large variations in physiological characteristics[8] — this line of research subverts the simplest picture of noise. That is that cells exploit noise when they need heterogeneity, and suppress it when they need deterministic, coherent behaviours.

This sea change in our perception raises an important and almost entirely unaddressed question. We know that cells can create virtually any type of noise; we also know that they can create almost any type of nonlinearity. What we rarely know, however, is which of the available strategies cells actually use. Is there a grander scheme that explains the choice between deterministic and noise-driven solutions? The only way to address this question experimentally is to characterize the single-cell dynamics of a large number of systems, and to see which strategies tend to be used to solve which problems. Given some reasonable physical constraints — mechanistic, energetic, evolutionary or otherwise — it may even be possible to partially answer the question from first principles. ■

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1. Zhou, T., Chen, L. & Aihara, K. *Phys. Rev. Lett.* **95**, 178103 (2005).
2. McMillen, D., Kopell, N., Hasty, J. & Collins, J. J. *Proc. Natl Acad. Sci. USA* **99**, 679–684 (2002).
3. Horsthemke, W. & Lefever, R. *Noise-Induced Transitions: Theory and Applications in Physics, Chemistry, and Biology* (Springer, Berlin, 1984).
4. Vilar, J. M., Kueh, H. Y., Barkai, N. & Leibler, S. *Proc. Natl Acad. Sci. USA* **99**, 5988–5992 (2002).
5. Raleigh, E. A. & Kleckner, N. *Proc. Natl Acad. Sci. USA* **83**, 1787–1791 (1986).
6. Ozbudak, E. M., Thattai, M., Kurtser, I., Grossman, A. D. & van Oudenaarden, A. *Nature Genet.* **31**, 69–73 (2002).
7. Elowitz, M. B. *et al. Science* **297**, 1183–1186 (2002).
8. Strogatz, S. H. *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering* (Perseus, Cambridge, MA, 1994).