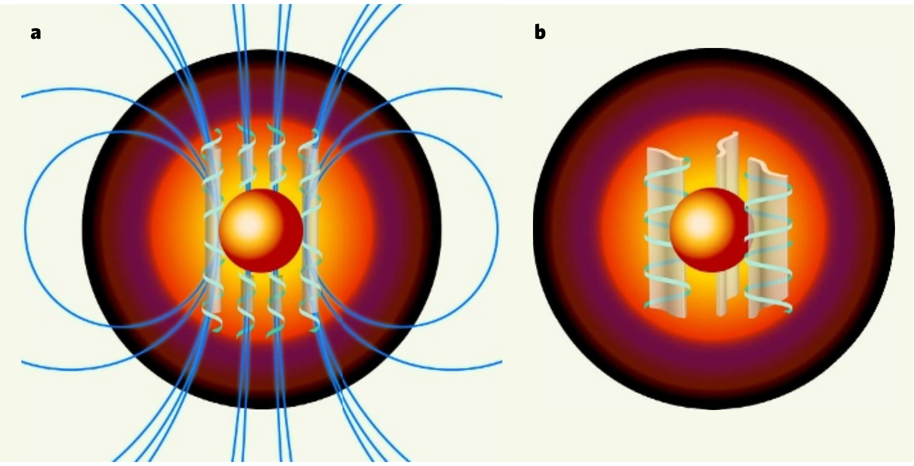

Figure 1 | Alternative geodynamos. The magnetic field is generated in Earth's liquid outer core. **a**, In the conventional concept, the molten iron circulates along a spiralling path in columns aligned in the north–south direction, generating electrical currents that set up the dipolar magnetic field. The concentration of field lines into anticyclonic vortices (rotating in the same direction as air around a region of high pressure) has been thought to explain the intense magnetic lobes found in Earth's field at the top of the core. **b**, The computer simulations of Kageyama *et al.*[1] show that the flow pattern in the core may bear more resemblance to a set of thin sheets, which puts the conventional concept into question. The sheet-like flow is efficient at generating a magnetic field, but how it might lead to the dipole geometry of Earth's field is not yet clear.

radiating away from its stem. Similar patterns have been observed in laboratory convection experiments[6]. If the flow in Earth's core has the form of elongated sheets rather than columns, the interpretation of magnetic flux lobes at the top of the core must be reconsidered.

Kageyama and colleagues' simulations[1] show that a laminated flow pattern still acts as an efficient dynamo. The conventional way of visualizing dynamo simulations is to map the resulting magnetic field lines. In complex dynamos the result often looks like a bowl of spaghetti and is hard to interpret. Kageyama *et al.* instead map lines of electrical current to produce a more coherent image, showing a large number of structures similar to the coils used in electrical engineering. However, unlike the Earth, this model produces a magnetic field that is not predominantly dipolar.

It is disturbing that dynamo models with grossly simplified parameters reproduce Earth's field well, whereas this agreement degrades when conditions are made more realistic. Some proposed explanations for this discrepancy highlight the problems encountered when performing simulations at the edge of what is currently possible. Even though the simulation took many months to run, it covered only 2,000 years of modelled time. If the flow in Earth's core were to stop suddenly, the dipole field would take 20,000 years to decay and so a similar time scale might be needed to create the field from scratch, requiring computer runs of years rather than months. In addition, the Ekman number is not the only parameter that has had to be set at unrealistic levels in geodynamo models. For example, the ratio between viscosity and electrical resistivity (magnetic Prandtl number) is set to 1 in simulations, despite being about 10^{-6} in the core.

It will remain impossible to model the geodynamo at true core conditions for the foreseeable future. The recipe for getting models with an Earth-like field might therefore be to have the parameters 'wrong in the right proportions'. The question is then what relationships between parameters must be kept fixed as we approach more realistic values. Kageyama *et al.*[1] have penetrated territory previously inaccessible to simulation. The next step will be even more demanding: scouting this new terrain to identify the true path through parameter space to understanding. ■

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SYSTEMS BIOLOGY

Reverse engineering the cell

Nicholas T. Ingolia and Jonathan S. Weissman

Borrowing ideas that were originally developed to study electronic circuits, two reports decipher how yeast reacts to changes in its environment by analysing the organism's responses to oscillating input signals.

Systems biology has certainly caught people's attention. But when pressed to define precisely what it is, let alone how it will complement classic reductionist approaches, concrete answers can be hard to find. One immediate, practical contribution of systems biology is that it suggests new ways of interrogating cellular responses to stimuli, and provides a framework for understanding the results[1]. In this spirit, two papers[2,3] now borrow ideas from the theory of system identification — a formal strategy for building mathematical models of dynamic systems based on experimental data — to examine the response of yeast cells to changes in their environment. In both cases, the authors use microfluidics to control precisely the external stimuli and to quantify the cells' responses. The authors thus unravel some of the 'wiring' of the signal transduction networks that monitor these environmental changes.

Studies of gene regulatory networks typically measure the way in which cells respond to strong perturbations, such as changes in temperature or abrupt variations in nutrient concentration. Such marked changes are valuable for inducing signalling pathways and for identifying the molecules involved, but are not likely to be representative of physiological conditions. At worst, they might even give a distorted view of the normal function of the pathways. Fortunately, more nuanced approaches can help overcome these problems.

Engineers know that certain dynamic systems, such as electronic circuits, can be studied by measuring their response to stimuli that vary with a sinusoidal pattern[4]. In this approach, the response of the system is measured at different frequencies of periodic signals; well-developed mathematical methods are then used to convert this 'output' into a model of the inner workings of the system. The frequency dependences of two quantities are particularly informative: the amplitude of the response and the lag (phase difference) between the input stimulus and the output behaviour (Fig. 1, overleaf). This approach has previously been used to study bacterial movement in response to different frequencies of pulses of a chemical attractant[5]. But broader biological applications of the strategy have had to wait for technical advances that are only now coming into play — such as microfluidics and fluorescent cell reporters.

Enter Mettetal *et al.*[3], who report in *Science*

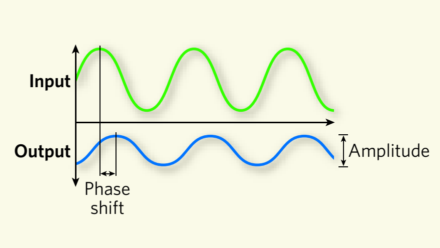

Figure 1 | Modelling dynamic systems. In systems such as electronic circuits, the input signals are transformed in a defined manner to produce the output. The output of the system in response to a sinusoidal input signal can be analysed with well-developed mathematical methods to produce a model of how the system works. The frequency dependence of two aspects of the output, namely the amplitude and the phase shift between the output and the input, is especially informative. This approach has now been used to model the biological pathways involved in the response of the yeast *S. cerevisiae* to glucose levels[2] or osmotic strength[3] in the surrounding medium.

their findings on the amplitude and phase responses of the yeast *Saccharomyces cerevisiae* to periodic changes in the osmotic strength of the surrounding medium. Using system-identification strategies borrowed from electrical engineers, they built an abstract model of the osmotic stress response from their data. They then compared this model with what was known about the molecular components of the response. This allowed them to reveal the role of different negative feedback loops in controlling the timescale of the process.

When starved of its favoured nutrient, glucose, *S. cerevisiae* can exploit an alternative sugar, galactose. In a study complementary to that of Mettetal and colleagues, Bennett *et al.*[2] (page 1119, this issue) have probed how the transcriptional regulation of the yeast's galactose-utilization genes responds to oscillations in glucose levels. These genes are induced by the presence of galactose, provided that glucose is not present.

Bennett *et al.* used microfluidics to produce a chamber that provides a controlled flow of growth medium to yeast cells. They then added glucose to the flow so that the glucose levels in the chamber varied sinusoidally. By studying cells that had been engineered to co-express a fluorescent reporter protein with one of the yeast's galactose-utilizing enzymes, the authors could quantify the cells' response to galactose. Using the microfluidics set-up, they were therefore able to measure the transcriptional response of galactose-utilizing genes to oscillations of glucose concentration at different frequencies. They found that the yeast reacts strongly to slow oscillations in glucose levels, but weakly to fast oscillations. The galactose-response pathway therefore seems to be a low-pass filter, in which cells react to long-term changes in nutrient conditions but ignore fast fluctuations.

The gene-regulatory response of yeast to galactose has been extensively studied, which allowed Bennett *et al.*[2] to use their results to make detailed, quantitative models of the biological pathway involved in the process. But their first model could not reproduce the scale of the difference between the low-frequency and high-frequency responses. The authors therefore proposed that a previously unsuspected mechanism, not included within their model, must also be involved.

Because the decay rate of messenger RNA in the pathway determines the duration of a crucial part of the model, and because glucose is known to affect the stability of some mRNAs, the authors hypothesized that regulation of mRNA stability by glucose could be the missing element of their model. They confirmed this experimentally, by showing that the mRNAs of critical galactose-response genes are destabilized by the presence of glucose. Bennett and colleagues' systems-identification strategy for studying the galactose-utilization pathway in yeast has thus led to the discovery of a previously unknown level of regulation in this well-studied process. Furthermore, the authors have linked the new regulation mechanism to a possible physiological function, namely responding to long-term changes in nutrients but not to faster fluctuations.

The authors next tested the response of a different strain of yeast — one that has a defect in its galactose-utilization pathway — to oscillations in glucose levels. This strain requires much higher levels of galactose than normal strains for steady-state activation of the relevant genes. They found that the defect affected only the phase component of the response to glucose oscillations. In other words, this strain was just as good as the normal strain at distinguishing different oscillation frequencies. Both strains are therefore capable of ignoring fast fluctuations in nutrients, but the mutant strain takes longer to respond to slow perturbations. Although otherwise accurate, Bennett and colleagues' simulations[2] of the defective yeast's response failed to predict that it would be slower to react than the normal strain. This might point to yet more unappreciated mechanistic nuances in the galactose-utilization pathway.

The experimental combination of microfluidic signal control with fluorescent output is powerful: any diffusible signal could, in principle, provide a variable stimulus, and fluorescent reporter proteins are a mainstay of modern transcriptional regulation studies. Frequency-response measurements of this sort will therefore be possible in many different biological systems. Of course, it might be that the systems-determination strategy will have limited use for interpreting the results, especially for noisy biological responses. But it should at least provide a starting point for unravelling pathways. More generally, these two papers[2,3] emphasize that the way we choose to perturb biological systems determines what aspects of those systems can be observed.

50 & 100 YEARS AGO

50 YEARS AGO

Bradenham Manor, the property of the National Trust, has been leased to the British Tabulating Machine Co., Ltd., for use as a Hollerith Computer Training Centre ... [T]he Centre was opened by Lord Halsbury ... who said that the old idea that a trainee learnt his job by copying what his predecessor could be seen to be doing has no room in the field of computer training. Training on modern, almost academic, lines is what is required ... Some 3,000 people per annum undergo training in the use and applications of mechanized accounting equipment at the five educational and training establishments maintained by the British Tabulating Machine Company's resources.

From *Nature* 30 August 1958.

100 YEARS AGO

A discussion will take place in Section D of the British Association on the abuses resulting from the strict application of the rule of priority in zoological nomenclature and on the means of protecting well-established names. Much inconvenience is caused by the extreme application of the rule ... the worst feature of which is ... the transfer of names from one to another, as we have seen in the case of Astacus, Torpedo, Holothuria, Simia, Cynocephalus ... Many zoologists think it is time to protest against the evil resulting from the indiscriminate application of what would be an excellent rule if tempered by a little consideration for tradition.

ALSO:

According to a *Times* correspondent, Dr. Lee De Forest expects that within two years Paris and New York will be in direct wireless telephonic communication. An apparatus which may ultimately transmit and receive messages to and from the Eiffel Tower is to be installed upon the 700-feet tower of the Metropolitan Life Insurance Company of New York.

From *Nature* 27 August 1908.

Technologies that permit a broader range of perturbations to be made should be welcomed, because they enable new aspects of even well-studied processes to be explored. ■

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CONDENSED-MATTER PHYSICS

Dual realities in superconductors

Tetsuo Hanaguri

In some copper oxides, superconductivity emerges when fixed electrons become mobile. A microscopy technique reveals that this process is associated with the transfer of electrons between real and abstract spaces.

Superconductivity is a dramatic phenomenon in which a material loses all resistance to electric currents. Although the concept is simple, the electronic states that underlie superconductivity are complex, and provide a rich area for research. This is especially true for high-temperature superconductors based on copper oxide (cuprates), for which mechanisms of superconductivity remain hotly debated some two decades after their discovery.

The properties of cuprates are mainly governed by the density of mobile charge-carrying species (such as electrons). This density can be controlled by 'doping' the material with small quantities of foreign atoms. As the number of carriers is reduced, the superconductivity of the material gradually diminishes, and a strange and poorly understood electronic state — the pseudo-gap state[1] — develops. On page 1072 of this issue, Kohsaka *et al.*[2] report a startling discovery in the nature of the electronic states that underlie this process. They find that, as carrier density decreases, the delocalized electrons responsible for superconductivity are progressively replaced by localized electronic entities, which form the structure of the pseudo-gap phase.

Conventional metals have many conducting electrons, which are best thought of as being spread throughout the material in waves. For all practical purposes, these waves do not interact with one another, which means that the quantum state of the electrons can be classified using a property (known as a wavevector) that is proportional to the electron's momentum. Electrons prefer to occupy low-energy states, but Pauli's exclusion principle allows only one electron to occupy any of the quantum energy states available in the metal. As a result, the lowest energy states are filled up to a characteristic energy level, so that every electron has its own definite momentum. The boundary between occupied and unoccupied states in the abstract space of momentums defines what is called the Fermi surface.

But in some materials, the approximation that electrons do not interact with one another breaks down. This leads to many interesting phenomena, none of which can be anticipated from the properties of individual electrons. Superconductivity is one of these emergent phenomena, and involves pairs of electrons bound together by an attractive interaction. When a sufficiently large number of these 'Cooper pairs' condense into a single quantum state, superconductivity occurs. In conventional superconductors, Cooper pairs consist of two electrons travelling in opposite directions at the Fermi surface. Superconductivity is therefore a phenomenon that is best understood in the world of momentum space.

In some transition-metal compounds, including cuprates, repulsive Coulomb interactions between the negative charges on electrons also have a role. In undoped compounds, Coulomb interactions are strong enough to localize an electron at each atomic site in real space, preventing the material from conducting electricity and so forming what is known as a Mott insulator. Doping Mott insulators with atoms that have additional charge carriers often leads to exotic phenomena such as high-temperature superconductivity.

How does the electronic structure of a cuprate change in the transition from a Mott insulator to a high-temperature superconductor? To answer this question experimentally requires the application of spectroscopic techniques that probe real space and momentum space simultaneously. Various techniques have been applied to cuprates, including angle-resolved photoemission spectroscopy (ARPES, which detects electrons emitted from materials that are irradiated with light) and scanning tunnelling microscopy/spectroscopy (STM/STS, which detects electrons that hop between the surface of a material and a sharp, electrically conducting probe). But ARPES can detect only momentum space, and STM/STS can detect only real space. At least, that was the case until now.

Kohsaka *et al.*[2] have used STM/STS to probe both real space and momentum space. In the presence of imperfections in materials, electrons (as defined in momentum space) scatter and interfere. As a result, standing waves of electron density are generated in real space that can be observed with STM/STS. The wavevectors of the standing waves can be precisely determined by Fourier analysis, thus providing a measure of the electronic structure in momentum space. Because of the unconventional

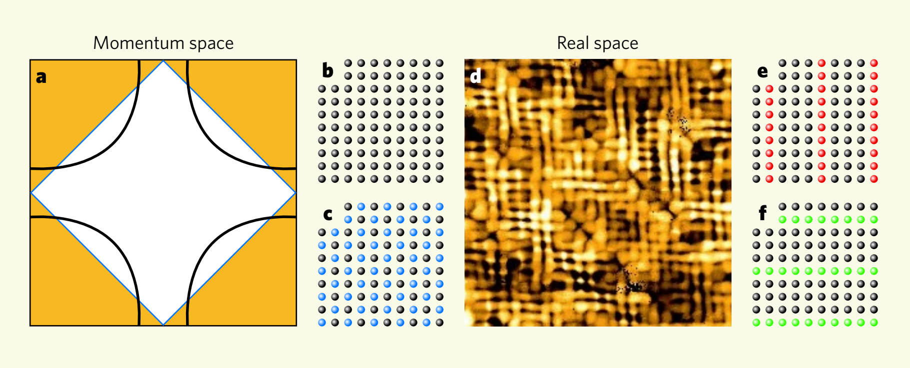

Figure 1 | Duality of electronic states in cuprates. a, The electronic states of a superconductor in momentum space are plotted here in two dimensions. The black curves denote the Fermi surface. Charges can participate in superconductivity only if they are located on regions of the Fermi surface that lie within the white zone. The yellow areas correspond to the region of momentum space in which the electrons adopt a pseudo-gap state. The blue line separating the superconducting and pseudo-gap regions is the extinction line. Kohsaka *et al.*[2] find that in a cuprate superconductor, this line does not vary with charge-carrier density. **b, c,** Assuming that the atoms of the superconductor are arranged in a grid (**b**), then a criss-cross pattern of electron states in real space (**c,** indicated by blue atoms) might explain the shape of the extinction line in momentum space. **d–f,** For the pseudo-gap state of their cuprate, Kohsaka *et al.* surprisingly observe a different pattern of electron density in real space — a mixture of horizontal and vertical domains. These might be explained by the electron periodicities shown in **e** and **f** (indicated by the green and red atoms). But why these should be so different from the arrangement shown in **c** is a mystery.