tetrathionate pathway at the same time as or after the acquisition of the T3SS, because Winter *et al.* find that the T3SS is required for tetrathionate-dependent replication. It could be that the recognition of the T3SS by the innate immune system led to the selection for acquisition of tetrathionate respiration by *S.* Typhimurium as an essential growth and colonization strategy. So this paper[2] further suggests that the evolutionary driving force for the inflammatory periods, which we call disease and which result from host–pathogen interactions, may be microorganism dissemination and transmission. By inference, intestinal pathogens may resemble their highly co-evolved counterparts elsewhere, such as infectious agents on the skin (herpes simplex virus) and airways (*Mycobacterium tuberculosis)*, that are responsible for chronic and episodic diseases for which the inflammatory periods are essential for transmission to new hosts.

Winter and co-workers' findings raise important issues about the unknown interactions between the microbiota, intestinal pathogens and their human hosts that could have a great impact on health. The challenge will be to develop technologies for monitoring the overall metabolism of each of these interacting components. By combining metagenomic analysis and modelling of the microbiota with functional studies of these microorganisms, researchers might be able to tap the rich source of information available within the human intestinal tract to better understand health and disease. ■

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COMPLEX SYSTEMS

Foreseeing tipping points

Theory suggests that the risk of critical transitions in complex systems can be revealed by generic indicators. A lab study of extinction in plankton populations provides experimental support for that principle. SEE LETTER P. 456

MARTEN SCHEFFER

On page 456 of this issue, Drake and Griffen[1] show that subtle changes in the pattern of fluctuations in a population can indicate whether that population is close to extinction. This is a step forward for conservation biology, but the wider implications are even more profound. The symptoms detected belong to a family of generic leading indicators that may help to determine whether a complex system is on the brink of collapse.

Although mathematical models often predict gradual trends of change quite well, we are still badly equipped when it comes to foreseeing radical transitions such as the crash of financial markets, the onset of severe droughts, epileptic seizures or the collapse of coral ecosystems. However, a new development in our ability to predict such events[2] stems from the insight that some dramatic shifts in complex systems may be related to the existence of tipping points (or 'catastrophic bifurcations'). As a system comes close to such a critical point, even small perturbations can trigger a massive shift, much as capsizing becomes increasingly likely as more cargo is loaded onto the deck of a ship. It is notoriously hard to know if a system is close to a tipping point. We simply do not see the 'brittleness' of the situation unless the transition happens.

The new approaches for probing the vicinity of a tipping point are based on the idea that, whereas the equilibrium state reveals little at all, non-equilibrium dynamics should change in universal ways in the vicinity of tipping points[2–5]. Thus, rather than looking at the state itself, we may have to look at its fluctuations if we want to know how vulnerable a system is.

The main principle behind this theory (reviewed in ref. 2) is the fact that systems that are close to a tipping point become very slow in recovering from perturbations (Fig. 1), a phenomenon known as 'critical slowing down'. The most straightforward implication is that system fragility can in principle be probed by studying its recovery rate following experimental perturbations[6]. As the test perturbations can be tiny, this may be done with little risk of causing the actual transition. For large, complex systems, it will often be difficult to systematically test recovery rates. But there is a way around that problem. Virtually all systems are permanently subject to natural perturbations. In such situations, it can be shown that, as a critical point is approached, critical slowing down will be reflected in characteristic changes in the frequency spectrum and variance of the fluctuations in the system (Fig. 1).

One such change is an increase in autocorrelation: subsequent states in a time series will become more alike. This phenomenon has been found, for example, in models of the collapse of ocean thermohaline circulation — the

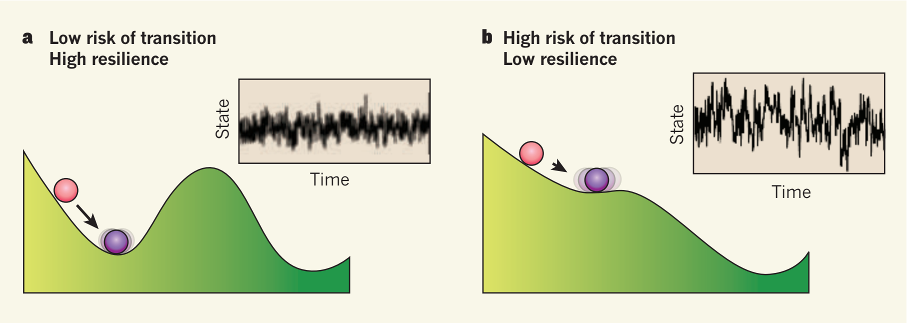

Figure 1 | Tipping points and leading indicators. The loss of resilience in the vicinity of tipping points can be understood from stability landscapes, shown here. **a,** Under conditions far from tipping points, a system is resilient: the basin of attraction is large, and perturbations will not easily drive the system towards an alternative state. **b,** If a system is close to a tipping point, the basin of attraction will be small, and a perturbation may easily push the system into an alternative basin. The state of the system by itself does not reveal such 'brittleness', but the system dynamics around the equilibrium differ in characteristic ways from those seen when the basin of attraction is large (as in **a**). In the risky state (**b**), the recovery rate from a small perturbation is slower (arrow), and the fluctuations in a stochastic environment will tend to be larger and more time-correlated, as shown in the insets. Such changes in dynamics are generic indicators for the proximity of tipping points, including those of the *Daphnia* populations investigated by Drake and Griffen[1]. (Modified from ref. 2.)

ocean's 'conveyor belt'[3,7]. But a systematic rise in autocorrelation has also been found before eight major climate transitions in the past[5]. Critical slowing down will also cause the correlation between linked units to rise as a tipping point is approached[8]. For instance, the correlation between financial markets may increase before a collapse, and the synchrony between neurons in the brain rises before an epileptic seizure[2]. Other leading indicators that may signal an upcoming transition are the rising variance[4] and skewness[9] of fluctuations.

The contribution of Drake and Griffen[1] is a landmark, as it reveals theoretically predicted signals in a controlled, living system. In a large replicated experiment, they exposed populations of zooplankton (*Daphnia*) to slowly deteriorating conditions in the form of declining food provision. The population displayed early warning signals, such as a rise in the coefficient of variation, skewness and autocorrelation, as much as eight generations before extinction occurred. Drake and Griffen's observations point to novel ways to judge population viability. Moreover, their demonstration of the practical detectability of generic indicators suggests that this approach might help to assess the risk of transitions in systems ranging from the brain to ecosystems, climate and society.

But we are not there yet. Plankton populations that are gently pushed to extinction under controlled conditions represent a particular case (a transcritical bifurcation). The critical point of no return in this instance is probably simply at a population size of one. In nature, populations often have a higher critical density that represents a tipping point (a fold bifurcation) beyond which numbers will enter free fall owing to the so-called Allee effect[10]. Theory predicts the same critical slowing-down symptoms in these situations. However, follow-up studies on a variety of controlled systems would help to give a broader view of how the critical phenomena will show up in practice.

At the same time, we may bridge the gap between the laboratory and the real world by mining data from the wide range of systems that occasionally go through sharp transitions. Detection of leading indicators is a notoriously data-hungry problem, and good, long time-series are difficult to obtain. But smart data-processing techniques[4,5,7] and analyses of spatial patterns[8,11] may help to reduce the lead time for warning. Still, reducing the chances of false negatives or false positives will be a challenge, and the risk of some kinds of transitions will simply remain impossible to assess.

From the perspective of managing single large systems such as climate, there is yet another issue[12]: even if we detect good early-warning indications, could we expect society to take timely action to turn a system back from the brink in the face of large uncertainty and the high costs involved? In other situations, the barrier to practical application may be lower. For example, if we are concerned about a particular endangered species, we may scan data on dynamics and spatial patterns for leading indicators to find out which populations seem closest to a critical point for extinction. Subsequently, conservation efforts could be targeted specifically at those populations.

Clearly, we have just scratched the surface in exploring the possibilities and limitations of this emerging field. However, the prospect of identifying generic indicators is exciting, as the approach may provide an independent way to assess the risk of critical transitions. Expansion of our toolbox for prediction is especially welcome given the almost insurmountable problem of modelling complex systems in a quantitatively accurate way. ■

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PHYSICAL CHEMISTRY

Seaming is believing

Do excited molecules relaxing to their ground state pass through a 'seam' connecting the potential energy profiles of the states? Experimental data suggest the answer to this long-standing question is 'yes'. SEE LETTER P. 440

TODD J. MARTINEZ

Most of the modern understanding of chemistry, including the very notion of a well-defined molecular structure, rests on the concept of a potential energy surface (PES) — a 3*N*-dimensional 'landscape' that plots the total energy of a collection of *N* atoms as a function of the atomic positions. The PES can be used to determine several useful features, such as the most stable configuration of atoms, or the pathway along which atoms 'travel' during a reaction. Intersections of these surfaces (known as conical intersections) are thought to have an important role in transitions from excited states to ground states of molecules, but direct evidence of this has been hard to find. Reporting on page 440 of this issue, Polli *et al.*[1] use ultrafast optical spectroscopy to follow the motion of the molecule retinal — whose light-induced isomerization forms the basis of vision — through a conical intersection. This provides much-needed experimental evidence of the involvement of conical intersections in de-excitations.

In order to define a PES, one must first invoke the Born–Oppenheimer approximation (BOA), which assumes that the electrons of an atomic system relax instantaneously to their lowest energy distribution. The electrons can then be taken out of the problem, so that the PES on which the atoms move becomes simply the electronic energy as a function of the atomic coordinates, plus energy contributions from the Coulombic repulsion of the positively charged nuclei. The success of the PES concept implies (correctly) that the BOA is normally an excellent approximation for molecules at room temperature.

The situation becomes dramatically different when electrons are excited, for example by absorption of a photon when molecules are exposed to light. Although the PES may remain a valid concept for some time after photoexcitation (the molecular motion of the excited electrons is simply governed by a different PES from that of the ground state), the electrons must eventually 'cool' and the molecule will return to the electronic ground state, violating the assumptions of the BOA. Because electrons are strongly quantum mechanical, this cooling is usually not a gradual energy transfer from electrons to molecular vibrations. Instead, it is often an ultrafast process that occurs most efficiently at molecular geometries in which two (or more) electronic states are isoenergetic[2,3]. Such geometries constitute conical intersections, and can be thought of as transition states in the relaxation of an electronically excited molecule. But unlike the transition states associated with ground-state reactions, conical intersections are not isolated molecular geometries. Rather, they are collections of geometries that form a high-dimensional 'seam', any point of which can serve as a doorway through which molecules may pass to reach the ground electronic state.