

fibroblasts, some cancer cells of epithelial origin^{6,7} and even in cells of different lineages in a single study⁸. What has been lacking, however, is a systematic comparison of the frequency of breaks at known fragile sites in different cell types from a range of organs and tissues. Yet it is known that *FHIT* and *WWOX* — the two genes at the two most fragile loci in lymphoblasts — are also among the sequences most frequently altered by DNA deletion in precancerous and cancerous cells of epithelial origin (that is, cells from internal organs, not lymphoblasts); this is presumably due to exposure of cells within lung, colon and breast to agents that cause replicative stress^{6,7}.

It has been argued that damage to genes at fragile sites, and the consequent loss of the genes' expression, contributes to the selective growth of precancerous lesions and cancerous tumours. A counter-argument is that, because of the frequent deletions within the fragile sites, the loss of any associated gene expression is an unselected 'passenger' event in cancers⁹ and does not drive the expansive growth of the cancer cells.

A comparison of the frequency of breaks at known fragile sites in a range of cell types, including the epithelial cells of the lung, colon, breast and prostate — where most human cancers originate — could shed light on several questions arising from the current study¹. For instance, are *FRA3B* and *FRA16D* the most fragile regions in these cells, as they are in lymphoblasts? If fibroblasts show infrequent DNA

damage at these sites, do they contain a different set of fragile sites, or do they show a low frequency of breaks across all chromosomes? Do the frequency and sites of breaks at fragile regions in cultured cells correspond to those in the same cell type within its organ of origin? Finally, if *FRA3B* is not the most fragile site in epithelial cells, does that strengthen the argument that breaks in *FHIT* in precancerous cells and cancers have contributed to progressive growth of the lesions? Undoubtedly, Letessier and colleagues, and indeed other scientists, will be searching for the answers. ■

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THEORETICAL ECOLOGY

Waltz of the weevil

The aquatic plant *Salvinia molesta* is a widespread pest of waterways in the tropics and subtropics. A study of its control by a weevil in Australian billabongs sets a new standard in ecological time-series analysis. [SEE LETTER P.86](#)

LEWI STONE

Waltzing *Matilda*, the bush ballad that became Australia's unofficial national anthem, relates the exploits of an out-of-control sheep shearer "camped by a billabong" (a small stagnant lake) in the Australian outback. On page 86 of this issue we read about the findings of an inspired group of theoretical ecologists¹ and their models of out-of-control billabongs. Schooler et al.¹ present a mathematical modelling study of an invasive plant species, the noxious weed *Salvinia molesta*, and its erratic large-scale outbreaks in four billabongs over a period of several decades. The authors' skilfully executed modelling is an imaginative combination of nonlinear dynamics, statistical inference and stochastic time-series analysis.

The story of *Salvinia* has become a classic in the biological invasion literature². This aquatic plant from South America is notorious for its rapid, almost uncontrollable growth, and since 1939 has become a pest in regions far from its home range. The weed is able to double its biomass every 3–4 days, generating thick mats of plant material that often cover entire water bodies (Fig. 1). *Salvinia* infestations can have devastating effects on lakes, billabongs and waterways, rendering them unusable for irrigation, as sources of drinking water or for sustaining local fish populations. In the past, entire villages in Papua New Guinea have been abandoned and the inhabitants relocated as a consequence of this out-of-control weed.

Salvinia first appeared in Australia's Kakadu National Park in 1983 and, within months, biological control was implemented by the



50 Years Ago

The Committee on Scientific Research in Schools which was established by the Council of the Royal Society in 1957 has issued a report covering the period November 1, 1959–October 31, 1960. It is stated that interest shown by schools in undertaking research has continued to increase, and the Committee is now administering research projects in 56 schools. Some of these schools have more than one research project under way and a total of 66 separate research projects are now being actively pursued compared with 57 last year ... All research projects with which the Committee is dealing are carried out with the specialist advice and assistance of Fellows of the Society and by others who act as advisers. The Committee invites further requests from school-masters and school-mistresses for assistance in undertaking research.

From *Nature* 4 February 1961

100 Years Ago

Many attempts have been made to synchronise the phonograph or gramophone with the kinematograph, so as to be able to reproduce simultaneously the sounds of the voice, as in singing and speech, while the movements of the face and the bodily gestures of the singer or speaker are depicted on the screen ... The difficulties, however, appear to have been surmounted by M. Gaumont ... The details of the method are not fully developed, but they are to be made public without delay ... We may soon have in our homes the *chefs-d'oeuvre* of our theatres played by our best actors, and even lectures by famous professors may not be restricted to their class-rooms ... Such reproductions are to be called *phonoscenes*.

From *Nature* 2 February 1911

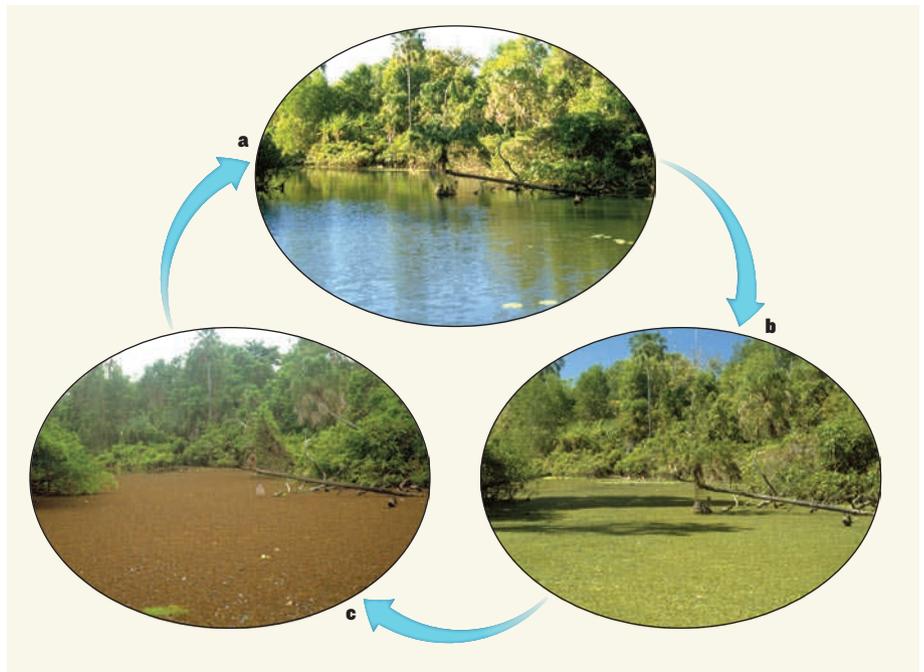


Figure 1 | *Salvinia* infestation of the Howard River, near Darwin, Australia. **a**, The scene before the advent of *Salvinia* in July 1984. **b**, One month later, with *Salvinia* rampant. **c**, February 1985, and the infestation is dying after attack by the weevil *Cyrtobagous salviniae*. Photographs taken by Colin Wilson (at risk of crocodile attack).

introduction of the weevil *Cyrtobagous salviniae*. Unusually, this beetle can feed on *Salvinia* possibly as fast as the weed can grow, causing the latter's dense mats to turn brown through decomposition (Fig. 1). In some cases the weevil can remove 99% of a large-scale *Salvinia* outbreak — which can comprise tens of thousands of tonnes of biomass — within a year.

Schooler *et al.*¹ elaborate on how the annual flooding of the billabongs further complicates the outbreak dynamics. Flooding tends to flush *Salvinia* downstream, allowing the pest to invade other billabongs or to find refuge in terrestrial sites. The ability of *Salvinia* to escape during flooding makes it almost impossible to eradicate the weed, despite the high efficiency of the biological control. Hence outbreaks recur, appearing at erratic and unpredictable intervals as they manage to evade the weevil's stranglehold.

The jumps from periods of control to periods of outbreaks have allowed Schooler *et al.*¹ to draw upon the powerful theoretical framework of alternative stable states, which has proved particularly relevant to those ecosystems in which abrupt changes and catastrophic shifts are intrinsic features^{2–4}. The authors were able to formulate the basic structure of a mathematical model that suits the *Salvinia*–weevil system. The nonlinear model has a deterministic 'skeleton' that is driven by environmental stochasticity, and takes into account the observed time-series measurement errors in *Salvinia* and weevil population abundance. But matching the model to the time series proved to be a formidable challenge. The high stochasticity and unpredictability of the billabong system,

combined with the complex dynamics introduced by periodic flooding, mean that, using most standard techniques, it is extremely difficult to interpret which of the different states the system is moving towards at any point in time.

Modern time-series analysis came to the rescue. Theoretical ecologists are familiar with the contributions of one of the authors (Ives) to ecological time-series analysis^{4,5}; Ives and his Australian co-authors now present¹ further innovation. More specifically, they make use of the (extended) Kalman filter, a statistical technique for which its inventor, engineer Rudolf Kalman, received the US National Medal of Science in 2008. The filter smooths out the system's stochasticity and, in parallel, provides an estimate of the model's statistical likelihood.

With such an estimate, it became possible to fine-tune the model structure by comparing a suite of different possibilities, while fitting the models to the observed billabong data. This allowed determination of the most reasonable model, and homed in on the best-fitting parameter estimates in a statistically rigorous manner. These methods are now finding exciting biological applications⁶, but in practice their complexity would normally call for the participation of a versatile mathematician. Hence the importance of multidisciplinary cooperation.

With the final model in hand, Schooler *et al.*¹ initiated a theoretical study of the nonlinear dynamics of its deterministic skeleton and investigated the existence of possible alternative stable states, and the manner in which they depend on control parameters. Two states were

identified: a low, *Salvinia*-free state, and a high state of dense *Salvinia* biomass. Under some conditions, these two stable states can coexist and population trajectories may be attracted to either state. Under other conditions there might be only a single state that is attractive. With flooding events and stochastic forcing, the system may be bouncing in a complex way between states, making it almost impossible to ascertain the underlying rules or patterns just by looking at the *Salvinia* or weevil time series.

The model that emerges from Schooler and colleagues' analysis¹ provides a useful tool for understanding the driving forces behind the *Salvinia*-weevil system — and its alternative stable states — that would otherwise be difficult to identify. With that as background,

the authors discuss how the modelling framework helps to suggest practical solutions for biological control. In particular, they argue that it may be possible to take advantage of the system's stochastic fluctuations and its associated erratic jumping between alternative states. In the higher state, when *Salvinia* biomass is at high density, weevil control is least effective. However, augmenting weevil control at those times when the system is attracted to its lower state might possibly trap the system into a stable *Salvinia*-free state. The model could thus help managers to identify the optimal time to apply biological control.

In all, Schooler and colleagues' careful attention to data, and their development and implementation of modelling techniques,

set a new standard in ecological time-series analysis. Their approach promises to have many applications in future studies of noisy biological data sets. ■

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GLOBAL CHANGE

Methane and monsoons

The rising trend in atmospheric concentrations of methane over the past 5,000 years has been attributed to human agency. A modelling study, of a power that has only now become possible, points to another cause. [SEE LETTER P.82](#)

ERIC W. WOLFF

Methane is a potent greenhouse gas, and influences the levels of other atmospheric constituents. The huge increase, of about 150%, to nearly 1,800 parts per billion by volume (p.p.b.v.) in atmospheric concentration over the past two centuries¹ is clearly caused by human activities. However, methane concentration also increased significantly, from about 550 to 700 p.p.b.v., over the previous 5,000 years — the later part of the (interglacial) Holocene epoch that began some 10,000 years ago. There has been intense debate about whether this rise was also anthropogenic or was due to changes in natural sources and sinks. Using models of climate, vegetation and emissions, Singarayer *et al.*² show how the increase could have arisen from natural causes (page 82 of this issue).

Detailed ice-core data for methane now cover the past 800,000 years³. They show a characteristic pattern over glacial–interglacial cycles, with higher values during interglacials. From the combined use of methane-concentration and isotopic data, it seems that the main cause of the glacial–interglacial rise was almost certainly an increase in the strength of wetland methane sources⁴, perhaps allied to a weakening of the atmospheric sink. Rapid fluctuations,

simultaneous with fast, millennial-scale climatic changes in the Northern Hemisphere, are also seen. Finally, the 'envelope' of data seems to follow closely the pattern of precession in Earth's orbit, which has a roughly 20,000-year cycle. The apparent reason for this is that tropical wetland emissions of methane respond to the amount of incoming solar

radiation (insolation) in summer at northern low latitudes. Insolation reaches its maximum during the part of the precession cycle when the elliptical orbit of Earth takes the planet closest to the Sun during northern summer. The result is a stronger monsoon in Asia and other regions, with more summer precipitation, and consequently greater wetland areas and methane production by soil-dwelling microorganisms.

However, the increase of the past 5,000 years departed from this pattern, with an increase in atmospheric methane concentration at a time when northern summer insolation was decreasing. In influential papers^{5,6}, Ruddiman proposed that the increase was due to human, especially agricultural, activity, which overwhelmed the variations in natural sources, even 5,000 years ago. There has been debate

about whether the much smaller human population of that period could really have had such a dominant effect. A strength of the hypothesis has been that the pattern of the past few millennia differed from that of earlier interglacials, which more closely followed the precessional insolation pattern.

Singarayer and colleagues' approach² involved an intensive modelling programme. To provide snapshots roughly every 2,000 years over the last glacial cycle, spanning 130,000 years, they 'forced' the Hadley Centre's HadCM3 coupled ocean–atmosphere general circulation model (GCM) with the appropriate orbital and ice-sheet configurations, and with greenhouse-gas concentrations, and ran the model to equilibrium. Other simulations were carried out, in which one or more of these forcings was held constant to isolate the causes of change.

The authors then fed the output of each climate simulation through a series of offline models

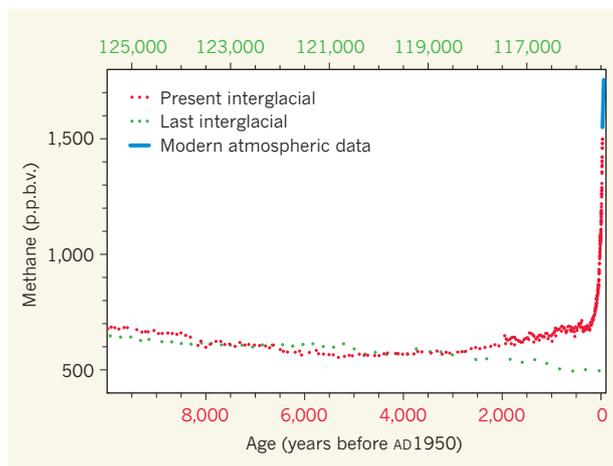


Figure 1 | Atmospheric methane concentrations during the present and last interglacials. Almost all of the data come from ice cores^{1,3}. The curves are for the past 10,000 years — the Holocene — and for the equivalent period (125,000–115,000 years ago, in terms of orbital precession) in the last interglacial. The red curve (with modern atmospheric data in blue) shows methane levels during the present interglacial, with a rise commencing 5,000 years ago. The green curve shows the contrasting continual decrease in methane during the last interglacial. Singarayer and colleagues' modelling study² can explain the trends in both interglacials in terms of Earth's orbit, except for the past 200 years, when a marked anthropogenic effect has occurred.