antibiotics does not necessarily mean that resistance will become a widespread problem. Antibiotic resistance often compromises the bacteria in other ways — for example, by reducing their growth rate[8]. This means that antibiotic-sensitive bacteria will outcompete the resistant forms when neither is exposed to the antibiotic. Perron *et al.*[1] investigated this possibility, and indeed found a 'cost' of antibiotic resistance: in the absence of the antibiotic, resistant bacteria took longer to start reproducing than control bacteria, although once they had got going, their replication rate was unaffected.

Unfortunately, bacteria have other tricks up their sleeves. In addition to adapting to antibiotics, they can also adapt to antibiotic resistance. There have been numerous cases of bacteria with antibiotic resistance developing mutations in other parts of their genome that compensate for the associated costs[8,9]. These adaptations are sometimes so specific that the growth rate of bacteria can decrease if the genetic changes conferring antibiotic resistance are replaced with the original sensitive form of the gene after compensatory adaptation has occurred[9].

Why should bacterial resistance to RAMPs cause more concern than resistance to other antibiotics? The major problem will be if resistance to chemotherapeutic RAMPs also confers resistance to naturally occurring RAMPs in humans and other organisms. Bacteria that are normally dealt with unnoticed by our innate immune system may then cause serious infections. Large-scale use of chemotherapeutic RAMPs may ultimately help pathogenic bacteria colonize parts of animals and plants that were previously off limits to them.

This perspective may be overstating the case for concern. Humans alone produce a highly diverse arsenal of RAMPs, which are also thought to be constantly evolving new ways of targeting bacteria[1]; and RAMPs constitute only one part of our natural immunity. Furthermore, RAMP resistance, where observed, is often specific to a small range of RAMPs[4]. There are exceptions, however. A variety of bacteria, including *Staphylococcus aureus* — famed for methicillin resistance — and the opportunistic pathogen *Pseudomonas aeruginosa* have evolved a degree of generalized RAMP resistance by increasing the amount of positively charged protein in their membranes. The consequence may be to reduce the binding efficiency of the positively charged RAMPs[10].

As Perron *et al.*[1], and others[2–4], emphasize, RAMPs are likely to make a major contribution to human health and agriculture. But given the prospect of resistance, extra caution is necessary in developing and using them. ■

Angus Buckling is in the Department of Zoology, University of Oxford, Oxford OX1 3PS, UK.
Michael Brockhurst is at ISEM, Université de Montpellier II, 34095 Montpellier, France.
e-mail: angus.buckling@zoology.oxford.ac.uk

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SEISMOLOGY

The start of something big?

Rachel Abercrombie

Can we predict the final size of an earthquake from observations of its first few seconds? An extensive study of earthquakes around the Pacific Rim seems to indicate that we can — but uncertainties remain.

How does a seismic fault, initially essentially immobile, start to slip at speeds of metres per second as an earthquake rupture front runs along it at speeds of up to 3 kilometres per second? Does the eventual size of an earthquake depend on the nature of this process? Or do all earthquakes begin in the same way, with the extent of rupture determined by conditions along the fault? Such fundamental questions get seismologists talking, because knowing how earthquakes begin is an essential part of understanding and modelling the dynamics of earthquake rupture, and may allow an earthquake's course to be predicted. Research until now has been inconclusive, but results described by Olson and Allen (page 212 of this issue)[1] imply that the final magnitude of an earthquake depends at least partially on what happens in its first few seconds. This timescale is equivalent to less than a tenth of the duration of the larger earthquakes in their study.

Research into the onset of earthquakes large and small has found that they often begin with small-amplitude shaking[2]. The interpretation of these initial 'sub-events' remains controversial. One model has it that a small, isolated subevent triggers a larger fault patch, which itself triggers further fault patches, and so on as long as sufficient energy is available. In this 'cascade' model, the beginning of a large earthquake is no different from the beginning of a small earthquake: therefore, predicting the final magnitude from the first few seconds is impossible. An alternative model is that the small

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Figure 1 | Finding fault. A view of the Lavic Lake seismic fault in California. The Hector Mine earthquake, one of those considered by Olson and Allen[1] in their study of the initial waves of Pacific Rim earthquakes, occurred along this fault line on 16 October 1999.

beginning is the last phase of some longer, slower, sub-seismic 'nucleation' process. (Such a process has admittedly never been reliably observed[3].) In this case, the final magnitude would be related to the nature of the nucleation process, and seismograms of large earthquakes would look different from those of smaller earthquakes right from the start.

Early warning systems currently in operation in Japan, Taiwan and Mexico use observations of the earliest-arriving primary (P) waves to provide a few seconds' warning of subsequent large ground motion — secondary (S) and surface waves — produced by the same earthquake. In an earlier study[4], Allen and Kanamori investigated the first few seconds of earthquake seismograms in southern California. They found that the predominant period (a measure of the frequency) for the first 4 seconds of the P waves provides a good estimate of the size of earthquakes with a magnitude M of less than 6. The duration of such earthquakes, defined as the time during which the fault actually moves, is usually less than 4 seconds (the waves generated by an earthquake last for much longer than the earthquake itself). Intriguingly, however, Allen and Kanamori's method[4] also predicted the approximate magnitude of three earthquakes of M greater than 6, and so an earthquake duration of more than 4 seconds. In other words, the final size of the earthquake could be predicted before the fault stopped moving.

Olson and Allen[1] set out to determine whether the final magnitude of the earthquake really does depend on the predominant period of the onset. They investigated the first few seconds of 71 earthquakes from California, Alaska, Japan and Taiwan, each recorded at multiple stations within 100 kilometres of the epicentres. Twenty-four of the earthquakes had a magnitude larger than 6, with durations of up to 70 seconds. Estimating the predominant period of the radiated seismic energy for each earthquake, the authors find that this value increases with magnitude for earthquakes of M between 3 and 8. This finding applies even to larger earthquakes in which the measurement is made after as little as a tenth of the earthquake's total duration — suggesting that the final magnitude of an earthquake is indeed determined a very short time after onset.

Previous studies of earthquake onsets have been limited by the lack of seismometers located close to the epicentre, and by the fact that standard techniques cannot analyse the frequency content of such short pieces of the seismograms. The method[5] used by Olson and Allen[1], and by Allen and Kanamori before them[4], is simple but effective. They calculate the predominant period from the ratio of the ground displacement to the rate of change of that displacement (the velocity of the movement) point by point. This measurement can be made as a seismogram is recorded, and at seismometers up to 100 kilometres from an earthquake's epicentre.

As Olson and Allen note, there is considerable scatter in their results; this leads to large uncertainties, especially in measurements at individual seismometers. An individual measurement of a predominant period of 1 second, for example, is consistent with an earthquake of any magnitude between 3 and 7.5. Most measurements of earthquake parameters vary significantly between seismometers, but even after averaging over many stations, any measurement of the mean predominant period produces an uncertainty of at least one magnitude unit. The predominant period of the 1999 earthquake in Hector Mine, California ($M = 7.1$; Fig. 1), for instance, is the same as that of an earthquake of M less than 5.

The relationship between the first 4 seconds of an earthquake and its final magnitude implies either that there is an initial, sub-seismic nucleation phase that is proportional to the size of the earthquake, or that any triggering cascade of sub-events lasts less than 4 seconds (the approximate duration of an earthquake of $M = 6$). But these observations of earthquake onsets are purely empirical, and we are far from understanding how onset, propagation and state of stress of the surrounding fault interact to determine the final size of a seismic event. Olson and Allen's study advances that understanding, and thus our ability to predict an earthquake's size before it reaches its peak. It also raises intriguing questions worthy of further study. ■

Rachel Abercrombie is in the Department of Earth and Planetary Sciences, Boston University, 685 Commonwealth Avenue, Boston, Massachusetts 02215, USA.
e-mail: rea@bu.edu

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CIRCADIAN RHYTHMS

Clock coordination

Michael N. Nitabach

Many animals concentrate their activity around dawn and dusk. This timing is regulated by distinct 'morning' and 'evening' oscillators in the central nervous system. But how are these two neuronal clocks coordinated?

A diverse range of organisms, from algae to human beings, have internal clocks that are synchronized to Earth's 24-hour rotation. When deprived of environmental cues, for example by being kept in constant darkness, these clocks 'free-run'; that is, they independently maintain rhythms of roughly 24 hours that gradually drift out of synchrony with Earth's rotation (hence their designation as circadian clocks). In animals, the clocks that control the timing of rest and activity are embodied in groups of neurons in the central nervous system.

One of the big questions in this field is how the oscillations of the multiple cellular clocks within an organism are coordinated. For example, the fruitfly *Drosophila melanogaster* possesses two anatomically distinct groups of clock neurons that can independently control its morning and evening peaks of activity[1,2]. Under normal conditions, however, the morning (M) and evening (E) oscillators run coordinately. On page 238 of this issue, Stoleru *et al.*[3] show that the M oscillator sends a daily resetting signal to the E oscillator to keep the two in synchrony.

Almost 30 years ago, it was theorized that nocturnal rodent circadian rhythms are controlled by independent, but coupled, M and E oscillators[4]. Later measurements of neuron firing in the rodent brain nucleus that contains the clock cells revealed two distinct subpopulations of neurons whose firing rhythms were out of phase, suggesting that these could be the M and E oscillators[5]. As with some nocturnal rodents, diurnal fruitflies show peaks of activity centred around the transitions from night to day and from day to night.

In previous work, Stoleru and colleagues[1] generated fruitflies that lacked either the lateral–ventral anatomical group of clock neurons or the dorsal group. Fruitflies lacking the lateral–ventral subgroup lost the morning peak of activity, but retained the evening peak. In fruitflies lacking the dorsal subgroup the reverse was true. Along with the results of Grima *et al.*[2], published simultaneously, these findings localized the M and E oscillators to the lateral–ventral and dorsal clock neurons, respectively.

Those experiments were performed in 12-hour:12-hour light:dark (LD) conditions, in which both oscillators can be independently synchronized to the environment and thereby maintain a constant phase relationship. When fruitflies are synchronized to LD cycles and then released into constant darkness (DD), the morning and evening peaks still occur — although they free-run and so gradually drift out of phase with the rotation of Earth. But