last step in the ribosome catalytic cycle, and each such cycle of addition of one amino-acid residue to the growing protein takes about 50 milliseconds. The ribosome spends most of this time sampling aminoacyl-tRNA adducts from the surrounding solution, searching for a fit between the current instruction (the codon) and an incoming amino acid. Incoming aminoacyl-tRNAs are complexed to another GTPase elongation factor called EF-Tu. Once a base-paired fit is established, EF-Tu shuttles the amino acid to an active centre that is occupied by the end of the growing protein, and then dissociates. EF-G then binds and does its job of ratcheting the tape.

Up until now, thinking about the mechanisms by which EF-G and EF-Tu might act has been coloured by the strong structural similarity between the GTP-binding domains of the two elongation factors and the GTP-binding domain of the one-protein Ras. Ras is a switch or, more properly, a relay, that flicks between a GTP-bound ‘on’ state, in which it binds to its target, and a GDP-bound ‘off’ state, in which it dissociates, according to a hormonal input signal. So the aspects of EF-Tu- and EF-G-mediated catalysis that have been emphasized are previously another GTP-dependent binding and GDP-dependent release steps. But during the past year new crystal structures of EF-Tu and EF-G have been solved, and they have revealed some big surprises.

First, the distal domains 4 and 5 of EF-G are seen to have the same shape and size as the tRNA binding partner of EF-Tu. This remarkable molecular mimicry suggests that the two elongation factors work using the same binding site. Second, the transition from GTP- to GDP-binding in the EF-Tu active site causes sizeable movement of the attached tRNA, encouraging models in which the tRNA of EF-Tu and the mimetic domain of EF-G act as mechanical manipulators — something like robotic arms.

So how is the putative mechanical action of EF-G coupled to the turnover of GTP? Rodnina et al. have used single-turnover experiments (in which the event of interest occurs only once) to show that GTP hydrolysis occurs five times faster than mRNA ratcheting. In other words, hydrolysis precedes translocation by quite a considerable time. The consequences of this finding are profound. It implies that the bond energy that is derived from the hydrolysis of GTP is stored in the protein, to be used later for mechanical work. The protein is like a compressed spring that is held against a trigger — ribosome-binding releases the trigger and the protein flies open, exerting force and allowing the phosphate that is generated as a result of GTP hydrolysis to exit from the active site.

There are striking parallels between this mode of chemical–mechanical coupling and the coupling that is used by the classical motor proteins kinesin, myosin and dynein (see figure). In these cytoskeletal motors, the product phosphate and/or the nucleoside diphosphate (ADP) are essentially trapped in the active site until the motor protein finds its binding site. The motor then adopts a strongly bound conformation prior to its mechanical power stroke. Rodnina et al. show that mRNA translocation is inhibited by mutagenic removal of domain 4 — the part of EF-G that mimics the tRNA of EF-Tu, whereas ribosome-activated GTP hydrolysis is unaffected. The implication is that the motor has lost its robotic actuator arm. Domain 4 is also required for the dissociation and recycling of EF-G: deletion of domain 4 leaves the motor stranded in the ribosome site, able to perform a single round of GTP hydrolysis but unable to dissociate. So the mechanical motion of domain 4 seems to be necessary to drive the motor into its dissociating conformation.

EF-G also gets ‘stuck’ if non-hydrolysable GTP analogues are used, emphasizing the fact that mechaanochemical coupling works both ways — just as active-site events can generate useful force, so active-site chemistry is sensitive to mechanical strain acting on the enzyme molecule. The challenge now, in all of these motor systems, is to set up experiments that measure two-dimensional rate constants for the linked mechanical and chemical equilibria, preferably at the single-molecule (single ribosome) level. Other words, we need to ask the question, “what happens to the active-site chemistry when I grab hold of this molecule and pull?”.

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**EARTHQUAKES**

*Long odds on prediction*

Ian Main

**EARTHQUAKES** and horse-racing are both complex phenomena where the prediction of individual events is inherently difficult, if not impossible. No one expects the bookmaker’s favourite to win every time, but no bookmaker ever expects the book to live long enough to make a calculation of the odds. But the perception of the public, the media and many government funding agencies is that we should nevertheless go on betting heavily on the prediction of individual earthquakes, rather than spending money on a careful calculation of the odds — that is, estimation of the seismic hazard.

A useful earthquake prediction requires specification in advance of the location, magnitude and time of an individual event, within narrow limits, otherwise a programmed evacuation could not take place. Prediction in this sense has proved elusive. In contrast, statistical estimates of the seismic hazard are based on a calculation of the likelihood of ground shaking from an understanding of the source mechanics of a population of earthquakes.

The thorny question of how to respond to the threat of earthquakes was at the core of a meeting* on the validation of schemes for earthquake prediction. Such schemes are sometimes based on a deterministic physical hypothesis, but more commonly on an empirical observation of geophysical or geochemical precursory ‘anomalies’. The most cited physical hypothesis was based on the observation of dilatancy (an increase in sample volume due to microcracking) and associated precursors observed in laboratory tests, proposed in the 1970s (ref. 3). But the predicted anomalies failed to materialize, and the hypothesis was rejected — that is, the results failed to scale linearly over the spatial and temporal scales that separate laboratory tests and large earthquakes.

At the meeting, consensus emerged on several points. First, given the dynamic complexity of earthquake sources and the material heterogeneity of the Earth, there are no clear reasons why the reliable prediction of individual earthquakes is possible. Second, we are not yet in a position to identify any significant and unambiguous earthquake precursors, even with the benefit of hindsight (‘past-posting’ in betting terminology). Third, individual predictions, and prediction methods, should be stated so that their success or failure can be objectively and unambiguously determined.

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*Assessment of Schemes for Earthquake Prediction, Royal Astronomical Society/Joint Association for Geophysics Discussion Meeting, London, 7–8 November 1996. Abstracts can be viewed at http://www.silso.demon.co.uk/Nov97/third_circular.html or are available by e-mail from russ.evans@lnd.ac.uk.

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Finally, in the absence of reliable prediction methods, we should concentrate on hazard mitigation based on a better understanding of earthquake source mechanisms, their statistical properties, the propagation of seismic waves and the response of individual sites, buildings and infrastructure to seismic vibration. This lower-profile statistical approach does not aim to give, say, a few hours’ or days’ warning for inhabitants of an area to leave it; rather, it results in guidelines for the construction of buildings and other structures that will withstand the forces earthquakes impose upon them. Most deaths and injuries from earthquakes are caused by collapse of buildings, or secondary effects such as ensuing fires, so this approach should save more lives, given the current state of knowledge.

Why have earthquakes proven so difficult or impossible to predict? There are two possibilities: either detectable and reliable empirical precursors do generally exist, but our instrumentation cannot measure them; or the physics of earthquakes is too sensitive to small fluctuations to produce reliable precursors. In fact, modern theories of earthquakes hold that they are critical, or self-organized critical, phenomena, implying a system maintained permanently ‘on the edge of chaos’, with an inherent random element and ‘avalanche’ dynamics with a strong sensitivity to small stress perturbations. The notion of self-organized criticality is consistent both with the observed frequency–magnitude relation of earthquake populations, and the presence of 1/f (power-law) noise in almost all borehole spectra on a variety of rock types in different tectonic areas (P. Leary, Univ. Edinburgh).

Evidence of ‘fracture criticality’ has been inferred from observations of seismic anisotropy, using a new theory of stress-induced, directionally dependent, contemporaneous crack opening and closure, which need not produce large-scale dilatancy (S. Crampin and S. Zatsepin, Univ. Edinburgh). Time-varying anisotropy due to stress changes may therefore be observable in the form of temporal changes in shear-wave polarization. This approach constitutes a middle course, where a full earthquake prediction is not possible, but the probability of occurrence of possible events is temporarily elevated above the long-term seismic hazard.

According to one view, it is “highly unlikely” that reliable precursors exist (R. Geller, Univ. Tokyo). Indeed, no single precursor satisfying the validation criteria developed by the International Association for Seismology and Physics of the Earth’s Interior has ever been observed unambiguously (D. Booth, British Geological Survey). These criteria include a precise definition of the anomaly, an explicit statement of the signal-to-noise ratio, detection at more than one site, and a full publication of negative as well as positive evidence.

There are many reported ‘anomalous’ electrical signals in earthquake zones, recorded as voltage oscillations between two electrodes coupled to the ground and separated by relatively long distances. Case studies of such observations were presented for Japan (Y. Enomoto, Mechanical Engineering Laboratory, Tsukuba, Japan) and Crete (F. Vallianatos, Chania, Crete). However, as in other descriptions of the same techniques, there is no clear-cut statistically significant correlation with individual earthquakes during the recording period.

In analysing such signals, it is also essential to be able to identify a plausible physical meaning for them — for instance, assignment of many electric precursors to events preceding an earthquake, notably by P. Varotsos et al. (the VANG group) in Greece, violates the principle of energy conservation (P. Bernard, Inst. Physique du Globe, Paris). It is an indication of mistaken priorities that earthquake ‘prediction’ as advocated by this group absorbs more funding than research programmes to improve building design practice in Greece (S. Stiros, Inst. Geology and Mineral Exploration, Athens).

Vague predictions, with loose limits on their magnitude, and time and place of occurrence, can also give spurious success rates, even for a purely random process (Bernard). This theme was taken up by several advocates of rigorous statistical testing and evaluation of the significance of reported precursors and predictions (Y. Kagan, Univ. California, Los Angeles; F. Mulargia, Univ. Bologna; P. Stark, Univ. California, Berkeley). For example, a prediction scheme should perform better than a naive rule, such as predicting that large events will have aftershocks (Stark, Mulargia). When this is done, with full access to the facts (successes — hits; and failures — misses or false alarms), it is hard to be optimistic about the prospects for reliable prediction. In contrast, methods already exist for assessing long-term hazard from combining instrumental, historical, geological and geodetic data (Y. Kagan; ref. 10).

Why is it hard to get this ‘negative’ conclusion, based on our experience of prediction, across? Speaking with the conviction of a prophet outside his adopted country of Japan, Geller laid into the sloppy practice and publicity-seeking activities of a minority of scientists and even non-scientists. We have had more than 100 years of failure in attempts to predict individual earthquakes, and “the public, media and government authorities must be clearly informed that earthquake prediction in its popularly understood sense is impossible at present, that all attempts to predict earthquakes to date have been failures, and that there are no reasonable prospects for prediction in the near future”.

Given the current state of knowledge, the best bet with a guarantee of return in reducing the threat from earthquakes is on hazard mitigation. Even then, it is likely that there will continue to be some failures. The next best bet, perhaps in the form of an each-way flutter, seems to be on the establishment of the possibility of a seismic hazard that may be time-dependent. In the absence of past-posting, the prediction of individual earthquakes remains a long shot.

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