

Figure 1 | Enzyme-catalysed isomerization. The enzyme ketosteroid isomerase (KSI) catalyses a reaction in which a carbon–carbon double bond in the substrate moves to a new position in the molecule. **a**, The side chain of an amino acid (red) in the active site triggers the reaction, which proceeds through a dienolate intermediate. Other side chains (green) stabilize the dienolate and the transition state that leads to it by forming hydrogen bonds (dashed lines) to its fully or partly negatively charged

oxygen. These hydrogen bonds also bind the substrate and the product, albeit more weakly. Curly arrows indicate electron movement during the reaction. **b**, Sigala *et al.*¹ investigate the control of KSI over the position of transition states during reactions, using phenolate ions as mimics of dienolates. Both the length of the carbon–oxygen bond and the electron density on the oxygen depend on the substituent X and on the bulkiness of the substituents R (R can be either hydrogen or fluorine).

on the oxygen changes at the same time.

According to the accepted mechanism for KSI-catalysed reactions, increasing the electron density on the oxygen of a phenolate should strengthen (and shorten) the hydrogen bonds that bind the molecule to the active site, and so reinforce binding to the enzyme. Sigala *et al.*¹ observe that this is indeed the case, but find that the pattern is disrupted if the phenolates are made slightly bulkier. When the hydrogen atoms attached to the carbons on either side of the oxygen are replaced by fluorine atoms (which are marginally larger and have higher electron density than hydrogens), increasing the electron density on the oxygen makes binding of the phenolate to the active site weaker, even though the hydrogen bonds should have been strengthened. This could be because the fluorine atoms start to clash (either electrostatically or physically) with the groups of the oxyanion hole as the hydrogen bonds try to become tighter, and thus shorter.

The crucial finding is that shortening of the hydrogen bonds by as little as 10 picometres is prevented by forces in and around the oxyanion hole, suggesting that the level of control exerted by the active site on the positions of its substrates operates on this stringently small scale. This result has wide-reaching implications: it defines experimentally the distance scale on which enzymes can distinguish geometric rearrangements of atoms, and determines the energetic consequences of this constraint. The picometre-precision of KSI also explains why protein engineering to produce enzymes that have new or altered functions has proved so difficult.

Sigala and colleagues' work brings one particular set of experimental tools to bear on a complex problem of fundamental importance, and will certainly concentrate the minds of those in the field. The same issue can and will be approached in other ways, and might well provide a range of answers that are specific to the system under investigation. We look forward to the development of a consensus. It will be interesting to see how other molecular

probes can be used to map out the furnishings of active sites and to define and compare the distance scales for catalysis. Meanwhile, the belief that electrostatic and geometric complementarity of active sites and transition states is central to enzyme catalysis has become better defined. And, to accept Feynman's implicit challenge, what we understand, we might one day be able to create. ■

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GLOBAL CHANGE

Climate's astronomical sensors

Michel Crucifix

A re-evaluation of the relationship between Earth's orbital parameters, ice-sheet extent and ocean circulation sets further puzzles for those trying to disentangle cause from effect in long-term climatic changes.

Earth's climate 'feels' the slow changes in the parameters of our orbit around the Sun. The great ice sheets of the Northern Hemisphere are one sensor, in that they are sensitive to the amount of solar energy they receive in summer. Lisiecki *et al.*¹ (page 85 of this issue) provide evidence that ocean dynamics also responds to orbital changes, and not just in the north.

Much of our life is controlled by the rhythms of days and seasons — not surprisingly, given that the Sun is our ultimate source of energy. Earth's atmosphere senses the rhythms of days and seasons, too, but both atmosphere and oceans may respond to the much longer astronomical cycles that affect incoming solar radiation. In 1976, Hays *et al.*² described how they tackled this problem. They collected deep-sea sediments in the Southern Ocean, dated them according to depth, and analysed the oxygen-isotope composition of the calcium

carbonate remains of foraminifera preserved in the sediments. This quantity is a proxy for ice-age conditions: isotopic composition indicates whether climate at any time was glacial — with large ice sheets in the Northern Hemisphere and low temperatures in the deep oceans — or interglacial, as today. Hays *et al.* then plotted this measure against time to estimate the frequency spectrum. Several of the dominant glacial oscillation periods they found corresponded perfectly to the astronomical periods calculated analytically by Berger³: 19,000 and 23,000 years for climatic precession; 41,000 years for changes in obliquity.

So, what are precession and obliquity? Earth revolves around the Sun following an elliptic figure. The climatic-precession parameter tells us what time in the year we reach perihelion — that is, the closest point to the Sun, when Earth is globally exposed to the maximum amount of incoming solar radiation. Perihelion is

presently reached on 3 January; it will be reached in July in 11,000 years and again in January in 22,000 years. Obliquity is the angle between the Equator and Earth's orbital plane. Changes in this angle are responsible for the seasons: the larger it is, the more energy the polar areas receive in summer. Neither precession nor obliquity modifies the total amount of energy reaching Earth in one full year. Only eccentricity — the orbital deviation from the circular — does that, but the effect is so small that it is neglected in most theories. Eccentricity does, however, modulate the amplitude of the effect of precession with periods of 100,000 and 400,000 years³.

Given that astronomical cycles hardly modify the global amount of incoming solar energy, the climate's astronomical sensors must be sensitive to the seasonal and spatial distribution of this energy. In that respect, the response of ice sheets immediately comes to mind. The amount of ice melting every year depends on the amount of solar energy absorbed during the warm season; the total ice mass is therefore expected to decrease when obliquity is high and perihelion is reached around summer. As early as 1876, John Murphy suggested that summer insolation could control glacial cycles⁴. History records the name of Milutin Milankovitch⁵ as the father of this theory, however, because of the firm mathematical foundation he provided for it (although he missed some crucial aspects of the ice sheets' response⁶).

But candidate astronomical sensors other than ice sheets have been proposed, most notably in two papers^{7,8} published as part of the SPECMAP project, which aims to rationalize the chronology represented by different palaeoclimate records. These papers downgraded the Milankovitch mechanism to a second-order effect, and attributed the prime cause of glacial–interglacial cycles to the response of Arctic sea ice to northern summer insolation. This Arctic response would have led to the development of northern ice sheets through a somewhat convoluted causal pathway involving circulation in the North Atlantic Ocean and changes in the concentration of atmospheric carbon dioxide.

Several drawbacks have been identified in the SPECMAP model⁹, but Lisiecki *et al.*¹ have delivered the coup de grâce. They began by noting that SPECMAP was not supported by good palaeoenvironmental records of the

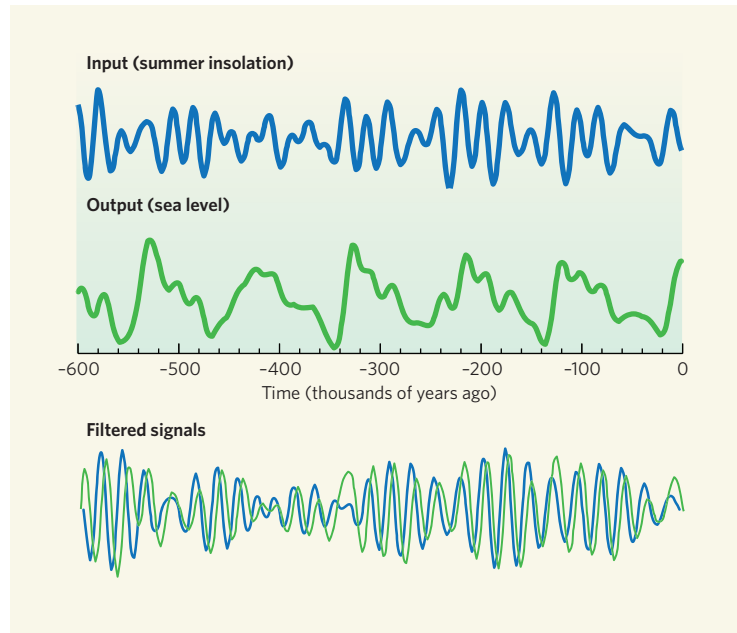


Figure 1 | Illustration of the linear signal analysis used by Lisiecki *et al.*¹ This example considers the output of a simple dynamical system (green, simulated sea-level¹¹) forced by a known input (blue, summer insolation in the Northern Hemisphere¹²). Both signals are filtered to extract their variance in a given frequency band (here, around 21,000 years, which corresponds to Earth's climatic precession). It is then verified that their phases, estimated by means of a Hilbert transform, are coherently related to each other. Such is the case here, with output lagging input by 1,500 to 6,500 years (90% confidence). This procedure confirms that the input effectively controls the system. But it does not guarantee that it is the cause of the large cycles in the output signal. In the artificial case tested here, these cycles are known to be autonomous: they would occur even without external forcing. The forcing simply acts as a clock, which has the effect of improving output predictability. Likewise, Lisiecki *et al.*¹ show that obliquity and precession control ocean circulation, but not the extent to which glacial cycles depend on this external forcing.

deep-ocean circulation. They instead used 30 archives of a naturally occurring isotopic indicator (the isotopic ratio of carbon in foraminifera shells) known to be sensitive to the distribution of water masses in the ocean. The archives are sufficiently broadly distributed geographically to provide a good idea of the global ocean circulation dynamics over the past 250,000 years.

Lisiecki *et al.* then essentially replicated the SPECMAP analysis procedure: band-pass filtering of time-series data to isolate the fraction of the signal thought to respond to precession and obliquity, and then assessing how this signal lagged the orbital elements (Fig. 1). The surprising result is that, when obliquity is high, the Atlantic Ocean tends to be dominated by deep water of Nordic origin — the opposite of the SPECMAP prediction. Moreover, when Earth is near its perihelion at the time of summer in the Northern Hemisphere, the Atlantic seems to be dominated by water of southern rather than northern origin.

With this, the view that the Arctic is the main 'front-end' orbital sensor of the climate system becomes hard to defend: the two orbital configurations (high obliquity and Northern Hemisphere perihelion) have the similar effect of increasing summer insolation in

the Arctic. How could they lead to opposite ocean responses? Lisiecki *et al.*¹ remark that things would be easier to explain if the ocean responded to summer insolation of the Southern Ocean, but we are left with conjectures to explain the mechanism. This is a challenge for those running general circulation models of the ocean and atmosphere.

Finally, another challenge merits mention. Lisiecki *et al.* used linear time-series analysis techniques to decipher the influence of orbital elements on climate. This is perhaps good enough to point out first-order effects, but climate is a nonlinear system. For example, it took about 100,000 years to build the big ice sheets that existed on the Earth of our mammoth-chasing ancestors, but those ice sheets largely disappeared within 10,000 years. That's not typical of a linear system. In fact, we are still unsure that orbital variations are necessary to explain glacial–interglacial cycles^{10,11}.

We need a more systematic way of developing and applying nonlinear statistical models to test our understanding of the slow dynamics of climate. The task is not straightforward —

how, for instance, do we rigorously account for dating uncertainties in sediments without becoming trapped in circular arguments (palaeoclimate scientists know this as the 'orbital tuning' problem)? Yet it is the only way to answer the crucial question of how far ahead glacial–interglacial cycles can be predicted. ■

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