kinase, ERK5. This finding implies that the signaling substrates "seen" and activated by the Trk receptors that bind neurotrophins differed according to whether signaling was local or retrograde. In contrast, the PI 3-kinase–Akt signaling pathway, which is essential for survival in response to NGF, is activated both locally and retrogradely by NGF (*2*). Interestingly, MacInnis and Campenot demonstrate that NGF immobilized on beads, which cannot be internalized, leads to activation of the PI 3-kinase–Akt pathway but not ERK1 and ERK2. This finding is similar to that seen when internalization of NGF (and presumably TrkA) is disrupted pharmacologically or by blocking the activity of dynamin, a protein required for endocytosis (*2*). Together, these findings dissociate the NGF survival signal—which does not require internalization of NGF but is dependent on PI 3-kinase—from NGF-TrkA signaling vesicles (*9*), which seem to be required for activation of ERK1 and ERK2 and may be more important for local responses such as growth (*8*).

The MacInnis and Campenot results are also relevant to how signals are transmitted in other cell types. In this regard, the requirement of receptor internalization for the activation of signaling proteins such as the ERKs has been previously noted in cells treated with EGF (*10*). The activated receptors, bound in clathrin-coated pits together with components of the endocytotic vesicle machinery, are directed to intracellular signaling proteins, culminating in the activation of the ERKs. A similar vesicle containing NGF, Trk, and Trk signaling proteins (including the ERKs) was recently characterized by Howe and colleagues (*9*). However, the MacInnis and Campenot work implies (i) that NGF can induce cell survival signals without the formation of signaling vesicles containing NGF, TrkA, and the ERKs, and (ii) that a second type of signaling pathway, potentially an activated Trk wave or a distinct type of vesicle, transmits PI 3-kinase–induced survival signals. Future studies determining whether NGF-beads can indeed stimulate the internalization of Trk, and whether the activities of different survival proteins are induced by NGF or NGF-beads, will help to elucidate these different potential pathways for survival signal transmission.

Whatever the nature of the activated TrkA retrograde signal, be it a new type of vesicle or a wave (or both), it is clearly different from the signal generated by local TrkA activation (see the figure). The TrkA retrograde signal can activate PI 3-kinase, but not ERK1 and ERK2. It is activated initially by NGF, but then is propagated and/or maintained in an NGF-independent fashion. Although these findings are surprising in terms of current biases, they are perhaps not as surprising when considered in terms of the biological necessity of signal transduction in a cell with the morphological complexity of a neuron. If you needed a receptor to maintain its activity while transported over long distances, then wouldn't it make sense to design it so that it could maintain its activation status in the absence of ligand? If you wanted one receptor to promote axonal growth locally, and then to promote cell survival at a distance, then might you not create multiple signal carriers specialized for these different functions? The MacInnis and Campenot report is not only important as a key addition to our understanding of how growth factors transduce long-distance signals, but it also provides us with a window onto possible new signaling pathways used by all cell types.

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PERSPECTIVES: PALEOCLIMATE

Cycles, Cycles Everywhere

Thomas J. Crowley

At the recent American Geophysical Union meeting in San Francisco, the 25th anniversary of one of the great papers in paleoclimatology was celebrated (*1*). The paper, entitled "Variations in the Earth's orbit: Pacemaker of the Ice Ages," presented important new evidence supporting the orbital theory of glaciation (*2*).

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Orbital theory goes back over a century but is most closely associated with Milankovitch (*3*), who calculated the effects of gravitational perturbations on the seasonal cycle of Earth's insolation (the radiation incident at the top of the atmosphere). Insolation varies on several time scales, including ~20,000 years (termed precession), ~40,000 years (obliquity or tilt of Earth's axis), and ~100,000 and ~400,000 years (eccentricity of Earth's orbit around the Sun). Together with the geographer Wladimir Köppen, Milankovitch hypothesized that glaciations occurred when Northern Hemisphere summer insolation was lowest. However, incomplete land records and poor chronology prevented them from fully testing their hypothesis.

In their 1976 paper, Hays *et al.* reported new evidence for the Milankovitch imprint from a deep-sea core. Advances in the chronology of deep-sea cores and the high resolution of their data allowed them to detect the precession, obliquity, and ~100,000-year eccentricity orbital periods in marine records. Although the precession and obliquity responses were linearly related to orbital forcing, there was a much larger nonlinear response to the relatively weak eccentricity forcing. The initial reaction to the paper was very positive, but some concerns were raised about the possible circularity of tuning the time scale of the core to optimize the fit to orbital forcing. This skepticism faded as evidence for a widespread imprint of orbital cycles in the geologic record mounted (*4*).

In the 25 years since the publication of (*2*), the importance of Milankovitch cycles has penetrated many areas of paleoclimatology. For example, John Kutzbach (University of Wisconsin) summarized evidence that orbital variations are now recognized to exert a strong influence on tropical climates, especially the monsoon system. Jean Jouzel (Laboratoire des Sciences du Climat et de l'Environnement, Gif sur Yvette) highlighted the importance of ice cores, which record the orbital imprint in the ice system and have provided exciting insights into the effect of trace gas changes (such as carbon dioxide and methane) on ice volume.

Virtually all credible models of ice volume change in the Quaternary [which began 1.8 million years ago (Ma)] require carbon dioxide changes to reproduce the observed record. Richard Peltier (University of Toronto) suggested that this link is so important that we may not see future ice volume increases until the present anthropogenic perturbation has been neutralized by the natural system (a process that is likely to take more than 10,000 years). According to Peltier, the magnitude of the anthropogenic perturbation may mark the

The author is in the Division of Earth and Ocean Sciences, Nicholas School of the Environment and Earth Sciences, Duke University, Durham, NC 27708, USA. E-mail: tcrowley@duke.edu

end of the Quaternary (the perturbation is so large that the climate system may not settle back into its previous pattern of oscillation even after the anthropogenic CO_2 effect is reduced to its background state).

Over the past 25 years, a vast array of high-quality and high-resolution Quaternary and pre-Quaternary records has been collected by the Ocean Drilling Program. These data, and some classic land sections (see the figure), have helped scientists to stitch together a near-continuous orbital-scale chronology for the past ~40 million years, allowing much more precise timing of important evolutionary and extinction events and better estimates of the timing and rate of climate change. For example, Nicholas Shackleton (University of Cambridge) reconfirmed an abrupt transition in the Miocene (~13.8 Ma) that was previously (*5*) attributed to quasi-permanent expansion of the Antarctic Ice Sheet. The transition now appears to be one of the best examples of abrupt climate change in the pre-Quaternary and presents an interesting target for modeling apparent instabilities in the climate system.

Example of orbital forcing in a classic nonmarine sequence. These ~12-million-year-old (Miocene) cyclic shallow lake sediments reflect astronomically controlled variations in lake level. Individual cycles (alternations between dark mudstone and white carbonate) reflect the precession cycle. Thick-thin alternations of carbonate beds in successive mudstone-carbonate cycles in the central, regular part of the section reflect the obliquity cycle. The ~400,000-year eccentricity cycle is visible in the lowermost part of the section (dark interval). Photograph taken near the village Orera, northeastern Spain.

Some intervals of the Mesozoic (245 to 65 Ma) and even Paleozoic (544 to 245 Ma) have also yielded valuable information on the pervasiveness of orbital forcing and provided new insights into climate dynamics and the pace of biotic recovery from the Cretaceous-Tertiary (K-T) asteroid impact. For example, orbital theory predicts million-year time scale oscillations in addition to the ones already mentioned. But long geologic sequences have not been available for testing this prediction, and there are a number of uncertainties with respect to the uniqueness of the orbital predictions on this time scale (J. Laskar, Observatoire de Paris). Paul Olsen (Columbia University) and colleages have found such "grand cycles" in a 33-million-year sequence (~200 to 233 Ma) of Triassic-Jurassic lake deposits from New Jersey. Identification of these periods may not only help to constrain orbital calculations but could also provide insight into observed climate transitions on a million-year time scale. Strong ~100,000- and ~400,000-year eccentricity periods in the pre-Quaternary, before the time of large ice volume changes, appear to require some tropical feedback.

Despite the great progress in Milankovitch studies, a number of problems remain. Several models for the 100,000-year cycle have been proposed, which all seem to require a feedback involving the adjustment of the lithosphere to ice sheet loading (the slow response time of rebound essentially "traps" the ice sheet in the ablation zone once warming is initiated). There is no consensus, however, as to which is the correct model.

The transition, about 1 million years ago, from dominant 41,000-year obliquity variations to the 100,000-year cycle also eludes a consensus explanation. The cause may be a threshold effect in the response of the system to external forcing (such as CO_2 changes) or to gradual changes in terrain elevation in areas of ice sheet inception. Because threshold changes can be triggered by almost any small perturbation, it may be more productive to study the internal physics of the system than to search for a trigger.

Similarly, there is no consensus on what causes ice-age CO_2 changes. The sheer number of explanations for the 100,000-year cycle and for CO_2 changes seem to have dulled the scientific community into a semipermanent state of wariness about accepting any particular explanation. This places a great burden of proof on proponents of any particular theory; any explanation seeking consensus acceptance must at this stage be characterized by mathematic completeness and predictability against a wide array of geological data. Most importantly, the explanation should be falsifiable—a step sometimes neglected in this and other fields.

Over the years, doubts have been raised about the basic validity of the orbital forcing mechanism and the role of eccentricity in the 100,000-year cycle. Many of these challenges are related to the orbital tuning approach for establishing chronologies. An impressive test of the tuning approach (*6*) was the prediction that the ages of the Brunhes-Matuyama and other paleomagnetic boundaries were incorrect by several tens of thousands of years. Argon-argon dating methods subsequently verified these predictions.

It is hard to believe that the standard model for Quaternary climate could be wrong and yet allow such sterling predictions. Nevertheless, high-precision dating of coral reef terraces (and other records) for the last interglacial (*7*) suggests that relatively high sea level occurred ~136,000 years ago—several thousand years earlier than predicted by orbital tuning. The results suggest an unusual and almost uncomfortable level of complexity in the interactions between orbital forcing and the climate system for at least some deglaciations. The tropical oceans may well be involved in these interactions.

Other dynamical interactions between orbital forcing and climate, such as the connection between large, orbital-scale ice volume fluctuations and smaller, rapid changes of climate on millennial time scales, are also understood incompletely. A few explanations have been offered for these rapid changes, but again there is no consensus.

On the tectonic time scale, the continuous marine chronology will likely be extended beyond the K-T boundary into the Mesozoic and will increasing be linked to high-resolution records on land. Among the many benefits to be gained by this effort will be an opportunity to determine whether there is a connection between evolving tectonics and temporal variations in the climate system response to orbital forcing. For example, Tibetan-Himalayan uplift may affect the amplitude and phase of the monsoon system's response to orbital forcing, and the opening and closing of ocean gateways (such as the central American isthmus and the Drake Passage) are likely to affect ocean heat transport and high-latitude climate change.

These problems and new data should keep scientists busy for another 25 years. By that time, perihelion of the Earth's orbit will have crept another 8 hours closer to the Northern Hemisphere summer solstice. The durability of the Milankovitch hypothesis will then be even easier to measure on astronomical time scales.

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