

tion of any one molecule will change substantially with time.

The experiments of Deschenes and Vanden Bout (6) are a dramatic confirmation of spatially heterogeneous dynamics near the glass transition. Using an optical microscope, they isolated the fluorescence of individual dye molecules in a polymer film a few degrees above T_g . Fluorescence was detected simultaneously for two different polarizations, allowing the orientation of the dye molecule's transition dipole to be measured in real time. Individual dye molecules were observed to reorient hundreds of times before they stopped fluorescing (because of photochemistry). Deschenes and Vanden Bout report that the rate of reorientation of individual molecules differed by more than a factor of 10 and that, for a given molecule, the rate can change substantially with time. For example, one molecule reoriented more than 100 times with a given rate and then suddenly changed to a different reorientation rate. Presumably, the dynamics of a particular molecule can change either because its environment evolves or because it moves from one region to another (see the figure on the previous page).

The concept of dynamic heterogeneity can be quantified in the following manner. Assuming that the system is ergodic (that is, a single molecule explores all possible configurations and environments given an

infinite amount of time), if one could measure the orientation of a single molecule for long enough, its time-correlation function would be identical to that from the ensemble average over all molecules. Over a finite time window, a time-correlation function can still be defined from a single-molecule trajectory if in this finite time the molecule has reoriented many times. Using this procedure, Deschenes and Vanden Bout observe that the time-correlation functions of different molecules are different, showing that on the time scale of thousands of seconds, the dynamics are heterogeneous. This heterogeneity may arise from slight variations in density, local packing, or the local energy landscape.

It would be of great interest to see how the distribution of time-correlation functions (obtained from a large number of single-molecule experiments) depends on the time window and the temperature of the system. This information, which cannot be obtained from ensemble experiments, is ideal for discriminating among models of dynamic heterogeneity. In particular, it will be interesting to see if the time-correlation functions become exponential as the time window decreases (the results of Deschenes and Vanden Bout suggest that they do) and, if so, to obtain information on the lifetimes of regions of different mobility, a matter of considerable importance and controversy (10).

The single-molecule rotation experiments of Deschenes and Vanden Bout reveal, in a way that no ensemble measurement can, the intricate details of the molecular motions responsible for the glass transition—motions that correspond to atomic displacements of only a few angstroms. They demonstrate clearly the importance of heterogeneous dynamics near T_g . Future experiments on single molecules and meso-scale systems (11) will likely provide a comprehensive picture of this heterogeneity, which according to at least some models is fundamentally connected to the slow dynamics that cause the glass transition.

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PERSPECTIVES: SUN-CLIMATE CONNECTIONS

Earth's Response to a Variable Sun

Judith Lean and David Rind

“Since we are the children of the Sun, and our bodies a product of its rays ... it is a worthy problem to learn how things earthly depend on this material ruler of our days.” Thus wrote Samuel Pierpont Langley in *The New Astronomy* in 1898. But the “worthy problem” of how solar variability may affect processes on Earth remains unresolved after more than a century, despite the fact that it is of particular importance today because of its implications for global climate change. Even a modest influence of solar variability on Earth's climate alters the assessment of anthropogenic effects and their likely future impacts.

Recent investigations of Earth's sur-

face, upper ocean, and lower tropospheric temperatures and the sun's irradiance suggest that there is indeed a discernable influence of solar variability on global climate. This follows a decade in which connections between solar variability and climate were alternately pronounced and dismissed (1–3). But how solar variability is translated into climatic changes on Earth remains to be fully explained.

Solar irradiance varies slightly over an 11-year cycle. This cycle of the sun's magnetic activity alters its energy output, as well as the occurrence of sunspots, flares, and coronal mass ejections. Sunspots (see the dark regions on the solar disk in the first figure, next page) have been used to track fluctuations in the strength of the sun's 11-year activity cycle for more than 300 years. Variations that are approximately in phase with this solar cycle have now been detected in satellite records of global

temperatures in the lower troposphere as monitored by the Microwave Sounding Unit (MSU) since 1978 (4), in upper ocean temperatures since 1955 (5), and in surface temperatures, primarily from thermometer records during the past century (6). In recent decades, these 11-year temperature cycles had peak-to-peak amplitudes of 0.06° to 0.1°C. They coincided with directly observed total solar irradiance changes ΔI of 1.1 W m⁻² (0.08%) (7), which resulted in a climate forcing ΔF of 0.2 W m⁻², where $\Delta F = 0.7\Delta I/4$. For comparison, net climate forcing by anthropogenic sources is currently about 0.35 W m⁻² per decade (8). The solar cycle signal becomes increasingly apparent in the upper troposphere and stratosphere, where it persists in four decades of global temperature records with amplitudes that increase from 0.3°C at an altitude of 6 km to 0.9°C at 20 km (9).

Decadal-scale climate oscillations by themselves do not prove a solar connection. Such variations have been linked to other phenomena, particularly ocean circulation (10, 11). But confidence in the reality of the sun-climate connection has grown as quantitative relations are established between increasingly long and precise databases of global temperature and

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solar irradiance, on decadal and centennial time scales, in combination with sophisticated statistical detection techniques and focused climate modeling studies.

In the 22-year-long, space-based MSU global temperature time series, a solar cycle–related periodicity appears after careful removal of the much larger (by a factor of five) influences of the El Niño Southern Oscillation (ENSO) and the El Chichón and Pinatubo volcanic eruptions (4). Analogous cycles were detected in an ensemble of century-long surface temperature data sets when signal processing was used to simultaneously identify the fingerprints of solar, volcanic, and anthropogenic influences (6).

Observations of total solar irradiance made with high-precision space-based radiometers since 1978 have provided quantitative measurements of solar forcing during the MSU epoch and, in combination with historical proxies of solar activity, have facilitated the reconstruction of longer term forcing. Paleoclimatic reconstructions of surface temperature and solar irradiance, although less certain than direct observations, augment and strengthen the case for sun-climate relations. It has been speculated (12) that solar irradiance changes by a few tenths of a percent on centennial time scales, with resultant climate forcing of 0.5 to 0.7 W m^{-2} and that these changes are associated with fluctuations of about 0.2° to 0.4°C in preindustrial surface temperatures reconstructed from tree rings, ice cores, and corals (13). The empirical relation of “Little Ice Age” cooling and the lack of sunspots from around 1645 to 1715 (the “Maunder Minimum”) is a recent example of such an association.

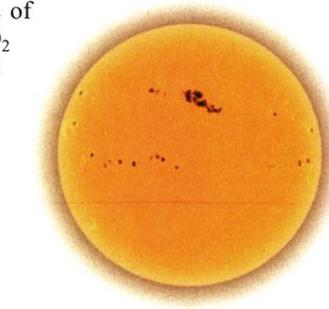
Various climate-modeling studies have used these temperature and irradiance results to explore the response of the climate system to direct and indirect solar forcing. Direct forcing in the troposphere occurs through solar changes primarily in the visible and near infrared spectrum (13, 14). A primary indirect forcing results from solar ultraviolet irradiance variations, which affect stratospheric ozone (15) and the mean winds. Ozone changes have a direct radiative impact on the troposphere, and altered mean winds affect planetary wave propagation from the tropo-

sphere and hence the natural modes of variability (16, 17). Observations have shown that descending large-scale circulation anomalies in the stratosphere influence tropospheric weather patterns (18). The fact that such mechanisms are seen in observations and have also been simulated in modeling studies of other forcings (such as CO_2 increase and volcanic aerosol injections) makes the solar variability influence less remarkable and more understandable.

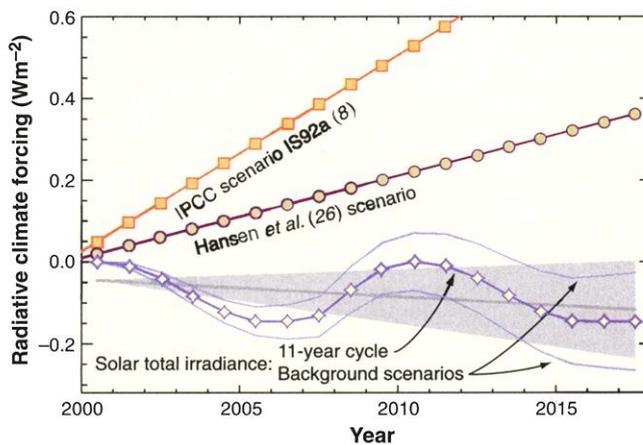
The apparent link between Earth’s temperature and variations in the sun’s irradiance implies that climate responds directly to solar forcing with a sensitivity of 0.3° to 0.8°C per W m^{-2} , approximately in phase with the solar forcing. Equilibrium sensitivities

the constraint that additional mechanisms seem not to be needed on the centennial time scale.

The increased temperature sensitivity at higher altitudes, where the amplitudes for the 11-year temperature cycles are larger than near Earth’s surface, may indicate an atmospheric dynamical response to solar variability, operating through interaction with the stratosphere. Other more esoteric mechanisms include the potential effects of global cosmic rays and energetic particles (both of which vary with the solar cycle) on cloud condensation nuclei and cloud cover. Unfortunately, existing cloud climatology records are too short to test these ideas, and suitable observations of the re-



The sun at its maximum. In this image, the dark regions are sunspots. The frequency of sunspot occurrence increases toward the solar maximum, when solar radiation reaching Earth is also enhanced.



Solar forcing in comparison with anthropogenic influences. Comparison of projected radiative climate forcings from total solar irradiance variations (diamonds) (25) and from anthropogenic sources [squares (8) and solid circles (26)]. Solid gray line, linear trend in the projected 11-year irradiance cycle (without any speculated varying background component); shaded regions, plausible range of background trends predicted from historical reconstructions.

from general circulation models (GCMs) are on the order of 0.7°C per W m^{-2} , so the magnitude of the solar variability signal in surface temperatures appears reasonable, at least on centennial time scales. But peak solar irradiance during a cycle lasts for only a few years. Accordingly, the climate is expected [from GCM studies such as (19)] to be less sensitive by a factor of 5 to 10 to forcing by the decadal solar cycle because ocean temperatures do not have time to fully respond. The apparent enhanced solar-climate sensitivity on decadal time scales thus requires further explanation, with

sponse of free tropospheric aerosol to solar-induced ionization changes are also lacking.

Solar forcing may also amplify internal oscillations (“noise”) in the climate system (such as ENSO) through processes such as stochastic resonance (20) or by exciting off-resonant responses in the delayed oscillator mechanism thought to be a component of many ENSOs (21). Given that ENSO modifies the climate of the continental United States (22), the long-standing empirical evidence linking U.S. drought to solar variability (23) may perhaps be explained by solar variability enhancement of natural climate variability modes in the Pacific. East African rainfall and drought reconstructions for the past 1100 years also suggest that hydrological parameters may be especially responsive to solar variability (24), perhaps associated with an ENSO-like amplification.

Sun-climate connections are clearly complex. The superposition of direct and downward-propagating effects and enhanced internal variability are expected to produce complicated regional fingerprints. This complexity may account for the varying strengths of 11-year and other solar-type cycles (solar activity also exhibits cycles near 80 to 90 and 200 to 210 years, for example) in many climate records and the difficulty in identifying sun-climate connections.

A firmer understanding of the impact of solar variability on the climate system offers numerous potential benefits. By virtue of the multiple processes and feedbacks involved, sun-climate connections provide a unique test for numerical climate models,

particularly their utility for predicting climate responses to future forcings, including anthropogenic effects. Understanding the linkages could facilitate use of the solar cycle in seasonal climate predictions if the magnitudes of the effect are found to be sufficiently large. Knowing how solar variability has altered climate in the past may help constrain the magnitude of anthropogenic warming and internal variability over the past century. It also provides a first-order indication of what may be expected because of solar variability in the future compared with other climate forcings (see the graph, previous page). If substantial greenhouse gas reductions are achieved, projected solar forcing may counter a substantial fraction of the remaining anthropogenic forcing in the next few decades,

providing unexpected complications for climate change detection when increasing certainty is expected and needed.

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PERSPECTIVES: NEUROSCIENCE

A Kinase to Dampen the Effects of Cocaine?

Amitabh Gupta and Li-Huei Tsai

Cyclin-dependent kinases (CDKs) are proteins that regulate the transition of cells from one phase of the cell cycle to the next (1). One surprising exception to this rule is Cdk5, which is not activated in dividing cells. Activity of Cdk5 is restricted to the central nervous system (CNS) and depends on Cdk5-specific activators, such as p35, which (in contrast to Cdk5) are expressed only in postmitotic neurons (2, 3). It is well established that Cdk5 is involved in both neurodevelopment and neurodegeneration. Exciting research from Paul Greengard's group now implicates Cdk5 in dampening down the neural changes in the CNS induced by chronic exposure to cocaine (4). The CNS usually adapts to chronic cocaine exposure by rendering the pathways that are stimulated by cocaine more resistant to the activity of this opiate. Greengard and colleagues show that Cdk5 is a crucial regulator of this adaptive response.

Mice deficient in the Cdk5 activator p35 are viable but suffer from an increased frequency of lethal seizures (5). Mice lacking Cdk5 have a more profound phenotype, dying shortly after birth (6). Histologically, both groups of knockout mice exhibit a layering defect in the neocortex of the brain that is believed to be

caused by defective migration and adhesion of neurons during embryonic development (7). This neocortical phenotype resembles the phenotypes of *reeler* and *scrambler* mice, but is distinct from them in that the preplate (the first collection of migrating neurons to form a cortical layer) is split at embryonic day 13 (7). The severity of the phenotype in the Cdk5-deficient mice is linked to anatomical defects that extend beyond the neocortex to many areas of the CNS. Because these defects also arise from aberrant neuronal migration and adhesion, Cdk5 clearly is involved in regulating these processes in the developing CNS.

Cytoskeletal components, adhesion molecules, and signaling proteins can all mediate Cdk5 activity (8–10). Recently, Cdk5 was found to induce the abnormal phosphorylation of tau protein, which resulted in the concomitant degeneration of neurons in disorders such as Alzheimer's disease (11). Intriguingly, this effect was promoted by calpain-mediated cleavage of p35 into p25, which then aided in relocating and stabilizing Cdk5 (12). Thus, in addition to driving migration and adhesion events in neuronal development, Cdk5 facilitates neurodegenerative processes under neurotoxic conditions. The dual functions of Cdk5 rejuvenate the connection between neurodevelopment and neurodegeneration (13).

Cocaine increases the amount of the neurotransmitter dopamine in synapses by inhibiting the dopamine uptake trans-

porter, which shuttles dopamine back into the nerve endings. In response to a greater supply of dopamine, dopamine-receptive neurons in the striatum become deregulated, resulting in the motor symptoms characteristic of chronic cocaine use. The deregulation of these neurons is accompanied by dopamine-induced activation of protein kinase A (PKA), which mediates the effects of cocaine by phosphorylating (adding phosphate groups to) a wide variety of proteins, including voltage-gated and ligand-gated ion channels (14).

A particularly important PKA target protein is DARPP-32, the dopamine and cyclic AMP regulated phosphoprotein (32 kD). Phosphorylation of amino acid threonine 34 by PKA allows DARPP-32 to bind to and inhibit the activity of protein phosphatase-1 (PP-1), which results in a diverse group of PP-1 target proteins remaining phosphorylated (activated) (see the figure, middle). Such targets include ion channels (some of which are also direct PKA targets) and transcription factors, for example, CREB (cAMP-responsive element binding protein). When phosphate groups are removed from Thr³⁴ in DARPP-32 by several phosphatases—particularly by PP-2B (calcineurin)—the DARPP-32-mediated inhibition of PP-1 is blocked, counteracting the effects of PKA. Thus, DARPP-32 may be viewed as a “molecular switch” that balances the opposing effects of PKA and PP-2B in order to regulate and fine-tune the phosphorylation state of PP-1 target proteins (see the figure, middle). Notably, mice deficient in DARPP-32 have increased motor sensitization to chronic cocaine administration (15). This finding suggests that the PKA–DARPP-32–PP-1 axis is likely to dampen the effects of chronic cocaine exposure, which stands in contrast to many

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