mine whether the oligonucleotide will ameliorate this effect. Another issue is whether redistribution of CUG^{exp} RNA introduces a different toxicity; RNA binding proteins that function in the nucleus may also have cytoplasmic RNA processing functions (*13*). This is the case for CUGBP1 and at least one member of the MBNL family (*14*, *15*). Because the mutant gene will produce toxic CUG^{exp} RNA for the life of the individual, treatment with oligonucleotides could last for decades and it might be best to get rid of the CUG^{exp} RNA altogether. One approach would be combined therapies such as the CAG25 oligonucleotide to release the RNA from nuclear foci and another differently modified DNA oligonucleotide that allows RNA degradation by endogenous ribonuclease H (*16*). This double-pronged attack could produce additive if not synergistic molecular effects and a desirable long-term therapeutic result.

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CLIMATE CHANGE

What Drives Climate Flip-Flops?

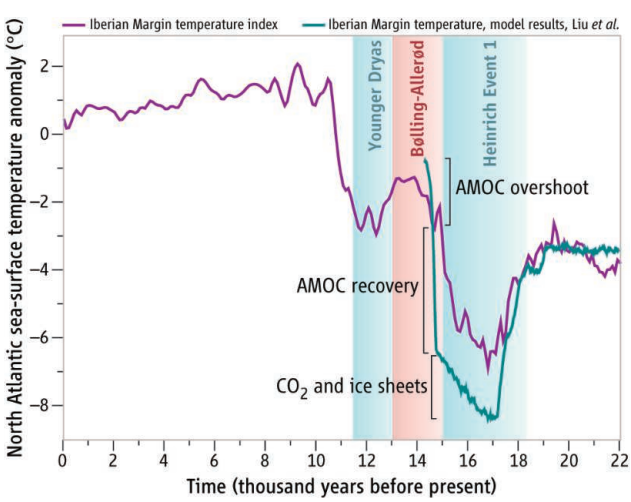
A numerical modeling study questions the validity of a key paradigm in rapid climate change studies.

Axel Timmermann and Laurie Menviel

The threat of rapid climate change concerns politicians and climate scientists alike. To assess whether abrupt transitions in the climate system are likely to occur in coming decades and centuries, an in-depth understanding of the conditions that led to past abrupt climate changes is required. On page 310 of this issue, Liu *et al*. (*1*) use a state-of-the-art general circulation model to investigate a poster child for dramatic climate events in recent Earth history: the Bølling-Allerød transition (see the figure). The results suggest that this transition can be simulated simply as the North Atlantic climate response to a rapidly ceasing glacial meltwater flow.

Around 14,600 years ago, the atmospheric circulation over the North Atlantic region flipped within just a few years to another state (*2*); also, Greenland temperatures skyrocketed by >10°C over several decades (*3*), terminating a cold phase known as Heinrich Event 1. The global impacts of this Bølling-Allerød transition have been well documented with climate proxy records such as sediment cores and ice cores, but the physical conditions that triggered the transition remain controversial. The temperature evolution from the Heinrich Event 1 to the Bølling-Allerød and the subsequent Younger Dryas cold phase (see the figure) is strikingly similar to the Dansgaard-Oeschger cycles (*4*) that dominated Northern Hemispheric climate between 60,000 and 30,000 years ago (*5*). Hence, unraveling the processes that triggered the Bølling-Allerød transition may also help to elucidate the mysterious, tantalizingly regular Dansgaard-Oeschger cycles (*6*).

In one of the most epic numerical modeling efforts of the climate community to date, Liu *et al*. have now set out to simulate the period from the Last Glacial Maximum (21,000 years ago) through the Heinrich event I and the Bølling-Allerød transition (see the figure). Prescribing the observed history of greenhouse gas concentrations from 22,000 years ago to 14,000 years ago, as well as time-varying solar insolation due to astronomical effects and reconstructions of ice-sheet topography and meltwater discharge, the equations of one of the most sophisticated climate models (CCSM3) were solved numerically on the Jaguar supercomputer at the Oak-Ridge National Laboratory. After about one-and-a-half years of number crunching, the first results (*1*) provide an unprecedented view into the mechanisms of the last glacial termination and the emergence of the Bølling-Allerød transition. The findings call for a paradigm shift in our understanding of abrupt climate change.



North Atlantic sea-surface temperature evolution. The simulated North Atlantic temperature in the Iberian Margin region (*1*) agrees well with a reconstructed temperature index obtained by averaging different alkenone-based sea-surface temperature reconstructions from cores SU-8118 (*13*) and MD01-2443 (*14*). The Bølling-Allerød warming can be decomposed into contributions that originate from the recovery of the Atlantic meridional overturning circulation (AMOC), an overshooting effect, and the climate response to increasing greenhouse gas concentration and shrinking glacial ice sheets.

Inspired by theoretical considerations (*7*) and idealized climate modeling results (*8*), previous attempts to explain abrupt millennial-scale climate change during the last glacial period—including Dansgaard-Oeschger events and the Bølling-Allerød transition—have relied on the idea that for a wide range of North Atlantic freshwater inputs, the Atlantic

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meridional overturning circulation (AMOC) has two different stable circulation regimes (*9*). According to this paradigm, abrupt climate change emerges as a flip-flopping between these equilibrium states. Liu *et al*., however, question the mere existence of this ocean "ambivalence" under glacial conditions.

By prescribing a Northern Hemispheric freshwater forcing scenario in which the discharge of meltwater from the retreating glacial ice sheets during Heinrich Event 1 stops suddenly, Liu *et al*. are able to simulate an abrupt recovery of the AMOC that triggers the transition from Heinrich Event 1 conditions to the Bølling-Allerød. The results are in good agreement with paleoclimate reconstructions based on climate proxy records. The rapid AMOC recovery described by Liu *et al*. also involves an overshooting effect (see the figure) that was noted in previous climate model simulations (*10*) and that affects mostly high-latitude climate in the Northern Hemisphere. Another contributor to the Bølling-Allerød warming is a 40 parts per million by volume increase in atmospheric carbon dioxide that accompanied Heinrich Event 1 (*11*) and further accelerated the deglaciation. Its origin remains a mystery.

The Liu *et al*. study initiates a new era of paleoclimate modeling. Previous paleoclimate modeling studies using state-of-the-art climate models adopted the time-slice concept to explore, for example, the climate of the Last Glacial Maximum or the mid-Holocene Optimum. In contrast, the transient modeling approach of Liu *et al*. simulates the climate evolution since the Last Glacial Maximum by prescribing the time evolution of the external boundary conditions based on astronomical theory, ice-sheet reconstructions, and the history of greenhouse gas concentrations. It thus offers the unique possibility to study the full spatiotemporal behavior of climate change, including the mechanisms of abrupt climate change, and to directly compare the resulting temporal features with paleoclimate data—for example, from sediment cores and ice cores.

However, such ambitious projects are computationally very demanding, and it might take several years before similar transient simulations can be carried out routinely with other coupled general circulation models. Even completing the CCSM3 simulation (*1*) by running it into the present will require another 2 to 3 million CPU hours on the Jaguar supercomputer.

Climate models are tools to promote our understanding of the climate system and predict its future evolution. Efforts to elucidate the complex mechanisms of past climate change will rely not only on the most realistic models such as the CCSM, but also on Earth system models of intermediate complexity that can explore Earth's long-term climate dynamics (*12*), and on conceptual models that have often initiated major shifts in our understanding of climate. Ultimately, breakthroughs in our understanding of Earth's climate evolution will come from close interactions between paleoproxy experts, paleoclimate modelers, and climate dynamicists. It is time to train a new generation of scientists familiar with all these fields.

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EPIDEMIOLOGY

Does Viral Diversity Matter?

Graham F. Medley[1] and D. James Nokes[12]

Detailed analyses of population demographics and viral diversity should help predict the impact of childhood vaccination for endemic viruses such as rotavirus.

Epidemic viruses, such as severe acute respiratory syndrome (SARS) and influenza A, cause diseases that rapidly spread to many people, and seem to attract more scientific and public attention than do endemic viruses, which are continually present in populations. Yet endemic viruses cause far greater disability and death. But epidemic viruses are endemic somewhere, or will become so, and endemic viruses are often recurrently epidemic. So developing a full understanding of the mechanisms that promote and drive endemicity is key to reducing the overall burden of viral disease and reducing the risk of future, widespread pandemics. On page 290 of this issue, Pitzer *et al*. (*1*) investigate the causes of epidemics of rotavirus, a major, global endemic virus.

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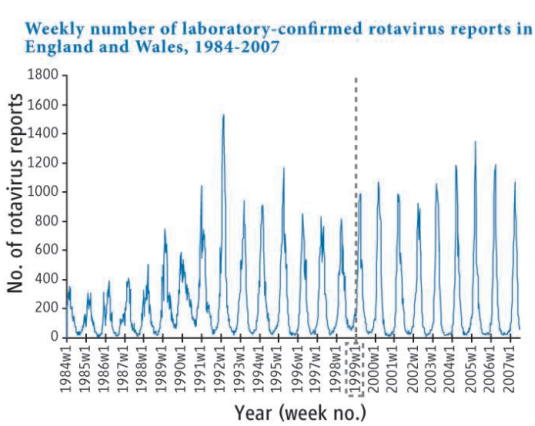
Rotavirus and respiratory syncytial virus are endemic viruses with epidemic propensity. They infect the epithelia of the gastrointestinal tract and respiratory tract, respectively, and cause severe childhood diseases. Both are RNA viruses (with a high propensity for genetic and antigenic variation) that occur in regular (mostly annual) epidemics (see the figure), infect children at a young age, and reinfect people throughout their lives. Disease is primarily associated with the first infection—acquired immunity reduces the severity of subsequent infections—but repeat infection is common and facilitated in part by viral antigenic diversity. New variants of rotavirus arise through mixing of its segmented genes during superinfection (simultaneous infection by two viral strains).

Innate and acquired immune responses severely limit survival of rotavirus and respiratory syncytial virus, so for a virus to persist, it must be transmitted to new, susceptible



Rotavirus regularity. Rotavirus occurs in annual epidemics. Shown are the weekly number of rotavirus reports in England and Wales from 1984 to 2007. The dashed line indicates that in 1999, most labs switched to antibody-based testing. The graph is taken from (*8*) with permission from Eurosurveillance.

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