in 100,000 years. Only for CO_2 concentrations less than 220 ppmv was an early entrance into glaciation simulated (*15*).

Such a long interglacial appears to have occurred only once in the last 500,000 years, at MIS-11 (*2*, *3*, *16*). At this time, astronomical insolation and some proxy climate indicators were similar to those of today. The CO_2 concentration was at an interglacial level [slightly above 280 ppmv (*8*)]. Simulations with these values (*16*) also show a particularly long interglacial, illustrating the importance of CO_2 concentrations during periods when the amplitude of insolation variation is too small to drive the climate system.

The present-day CO_2 concentration of 370 ppmv is already well above typical interglacial values of ~290 ppmv. Taking into account anthropogenic perturbations, we have studied further in which the CO_2 concentration increases to up to 750 ppmv over the next 200 years, returning to natural levels by 1000 years from now (*13*, *15*). The results suggest that, under very small insolation variations, there is a threshold value of CO_2 above which the Greenland Ice Sheet disappears (see the bottom panel of the figure). The climate system may take 50,000 years to assimilate the impacts of human activities during the early third millennium.

In this case, an "irreversible greenhouse effect" could become the most likely future climate. If the Greenland and west Antarctic Ice Sheets disappear completely, then today's "Anthropocene" (*17*) may only be a transition between the Quaternary and the next geological period. J. Murray Mitchell Jr. already predicted in 1972 that "The net impact of human activities on the climate of the future decades and centuries is quite likely to be one of warming and therefore favorable to the perpetuation of the present interglacial" [(*1*), p. 436].

This scenario will have to be confirmed with models that better simulate ice sheets and ocean circulation. Recent results by Peltier and Vettoretti (*18*) are encouraging. With the Canadian climate general circulation model, they showed that under the present-day insolation regime and preindustrial CO_2 concentration, no glacial inception is possible. In contrast, the model is able to simulate a glacial transition at the end of the Eemian.

Most model studies to date confirm that the pattern and range of global climatic conditions likely to be experienced in the future will be close to those during the warmest phases of the last few tens of millions of years. We must use the reconstructed record of these past climates to test our understanding of the behavior of the climate system and as a guide to future conditions.

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PERSPECTIVES: THERMODYNAMICS

Water and Ice

Alan K. Soper

To the nonspecialist, it must come as a bit of a surprise to discover how much scientific attention is paid to the apparently simple water molecule, H_2O. Almost every week, new results on water and ice appear in high-profile journals, while lesser molecules like hydrogen fluoride or ammonia seem to get little or no coverage.

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The apparent simplicity of the water molecule belies the enormous complexity of its interactions with other molecules, including other water molecules. In common with all other molecules, it experiences repulsive overlap and attractive van der Waals forces, but added to this is the strongly directional force of hydrogen bonding. A satisfactory description of this force still eludes scientists. In water, the strength and directionality of the hydrogen bond combine with molecular geometry in a way that sets this molecule apart from almost any other, giving water its complex and still poorly understood phase diagram (see the figure).

A well-known aspect of this phase diagram is the fact that at ambient pressure and 0°C (273 K), ice is less dense than water, and that the liquid is less dense at 0°C than at +4°C. In fact, if you supercool the liquid below 0°C at ambient pressure, it continues to become less dense (*1*). But this process does not continue indefinitely. At about –40°C (233 K), the liquid will spontaneously crystallize, no matter how pure it is (*2*). This temperature, known as the homogeneous nucleation temperature (HNT), is the cause of much controversy that remains unresolved.

But the plot gets even thicker. As water is supercooled, its diffusion constant diminishes, and appears by extrapolation to go to zero just below the HNT. This observation has led to the conjecture that there is a "stability limit" to the supercooled liquid (*3*). For water, however, this limit is not the usual glass transition temperature, as it would be for many other liquids. Instead, it represents the start of a region where disordered water apparently cannot exist. The glass transition temperature for water is in fact much lower, probably around 136 K.

One simple method of circumventing this "no man's land" in the water phase diagram is to take hexagonal ice at 77 K and pressurize it to about 2 GPa (*4*). This process leads to a dense form of amorphous ice, called high-density amorphous ice (HDA), which remains dense if kept below ~100 K. But if HDA is warmed to ~115 K, it suddenly expands to another form of amorphous ice called low-density amorphous ice (LDA). LDA appears to be similar in structure to the amorphous ice produced by vapor deposition and hyperquenching of the liquid.

The suddenness of the HDA-LDA transition was one of several factors leading to the conjecture that water exhibits a liquid-liquid critical point below which two different forms of liquid water coexist (*5*). This tantalizing suggestion, which was based on a computer simulation, went a long way toward explaining, at least qualitatively, many of the anomalous properties of water. It was, however, controversial, because the proposed location of the second critical point at 200 K was in the middle of the region where, according to the stability limit conjecture, bulk water can only exist in crystalline form.

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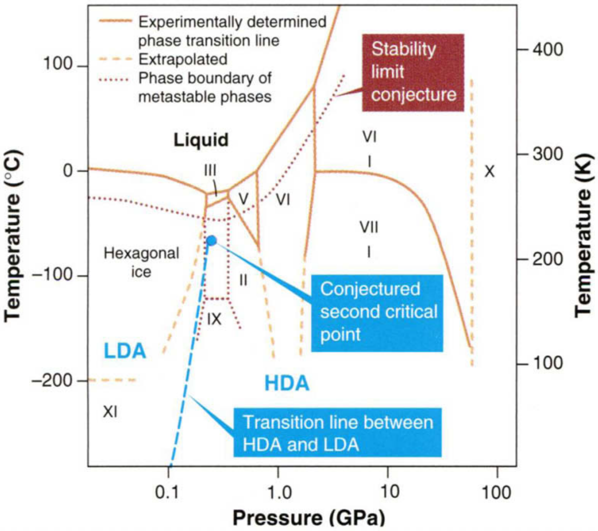

A simplified phase diagram of water. Roman numerals denote different solid phases of water

If there really is a liquid-liquid critical point in water, then the transition from one liquid to the other must be first-order, that is, discontinuous in density. If LDA and HDA are the low-temperature manifestations of these two forms of water, then the transition from LDA to HDA, or vice versa, must be sudden. But is the HDA-LDA transition really sudden, or does the structure relax in a stepwise fashion via a series of intermediate structures? Could the relaxation even be continuous? On page 1320 of this issue, Tulk *et al.* (*6*) provide experimental evidence for such a continuum. (Of course, if HDA and LDA are not the low-temperature forms of the two purported liquids, then there might be some new forms of water out there still to be discovered.)

Another known liquid water phase may provide some clues to the low-temperature behavior of water. In the stable liquid phase just above the melting point, the structure of water undergoes a characteristic and continuous transition from an open network structure at low pressures to a much denser form at high pressure. As the density increases, the tetrahedral arrangement of nearest-neighbor molecules found in ordinary water and hexagonal ice is preserved, as it is in many of the phases of ice. However, beyond the nearest-neighbor tetrahedron, the hydrogen bonds become increasingly bent or broken as the pressure (and hence density) is increased.

At the temperature at which HDA is stable, the transition from LDA to HDA cannot be induced directly, because the material is invariably in powdered form and hence the density cannot be increased continuously by applying hydrostatic pressure. Instead, Tulk *et al.* attempt to capture amorphous ice in its intermediate states by carefully annealing samples of HDA at different temperatures. After each annealing, they cool the samples to 40 K and measure their x-ray and neutron diffraction patterns. The results seem unambiguous: A whole series of intermediate (and possibly continuous) structures is found, and the diffraction patterns cannot be represented as a linear combination of the diffraction patterns of HDA and LDA.

In other words, the intermediate structures must be distinct from those of both of these amorphous ices. If this interpretation is correct, then HDA and LDA cannot exist as unique entities. Tulk *et al.*'s evidence for a continuous, or quasi-continuous, transition between LDA and HDA (*6*) makes it more difficult to support a thesis that there is some point in the water phase diagram where two distinct disordered forms of water can coexist.

Of course, one experiment does not resolve all the issues. The liquid-liquid critical point scenario has spawned many theoretical and experimental studies, and it does provide one of the first qualitative frameworks for describing water properties. Nonetheless, alternative scenarios such as that described in (*7*) can also be quite successful at predicting water properties. What is certain is that experiments like that reported by Tulk *et al.* (*6*) will provoke ever more incisive techniques for looking at water at the molecular level.

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PERSPECTIVES: NEUROSCIENCE AND EVOLUTION

Snake Sodium Channels Resist TTX Arrest

Raymond B. Huey and William J. Moody

> *...there is a constant struggle...between the instinct of the one to escape its enemy and of the other to secure its prey.*
>
> –Charles Darwin (*1*, p. 380)

Eye of newt is a necessary ingredient in a witch's broth, but skin of newt makes a better defensive toxin. Indeed, skin of the North American newt *Taricha* contains tetrodotoxin (TTX), a potent neurotoxin that paralyzes nerves and muscles by selectively blocking sodium channels. Armed with their toxic skin, these newts wander around brazenly during the day, safe from attack by hungry predators—safe that is, unless they live in parts of western North America. Here, garter snakes (*Thamnophis sirtalis*) dine readily on newts because they have evolved a marked resistance to TTX (see the figure). On page 1336 of this issue, Geffeney *et al.* (*2*) explore how these snakes avoid TTX poisoning and implicate voltage-gated sodium channels in muscle as the site of TTX resistance.

Salamanders are easy prey for snakes. Not surprisingly, many salamanders have evolved remarkable defenses (*3*). Newts of the salamander genus *Taricha* have taken this predator-prey arms race (*4*) to an extreme by sequestering TTX in their skin (*5*). However, newts are not the only organisms to use TTX in self-defense. They are accompanied by a phylogenetic smorgasbord of animals—*Fugu* pufferfish (see the Perspective on page 1283), *Atelopus* frogs, blue-ringed octopus, and *Phallusia* tunicates. But not all predators are deterred by TTX: Humans voluntarily ingest small quantities of TTX when dining on *Fugu* in Japan, and may ingest it involuntarily during voodoo rituals in Haiti (*6*).

Virtually all snakes die if they mistakenly eat a newt. However, a few populations of garter snakes have evolved a high level of resistance to newt TTX (*2*, *7*). These snakes readily eat newts, although their postprandial crawling speed is temporarily slowed. Resistance to TTX is variable (genetically and phenotypically) within garter snake populations. Importantly, resistant snakes are slower than their more susceptible counterparts, reflecting a negative genetic correlation (trade-off) between resistance and speed (*8*).

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