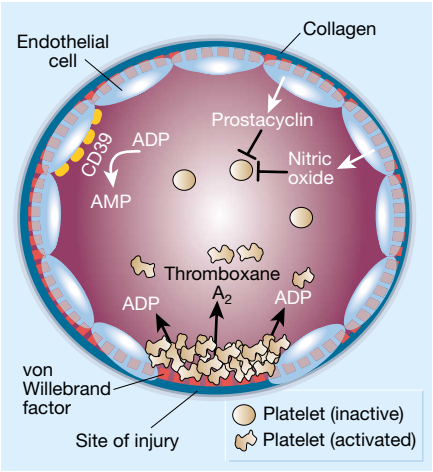

Figure 1 **Formation of a platelet plug at sites of blood-vessel injury. Top, circulating platelets are maintained in an inactive state by prostacyclin and nitric oxide, released by endothelial cells. Endothelial cells also express on their surface CD39, an enzyme that converts to inactive AMP any small amounts of ADP that might otherwise activate platelets. Bottom, at sites of vascular injury, endothelial cells are damaged or removed. This exposes collagen fibrils, to which platelets adhere with help from von Willebrand factor, a blood protein synthesized by endothelial cells. Once activated in this way, platelets secrete ADP and thromboxane A_2. These molecules bind to receptors on circulating platelets, causing them to change shape and become activated, and recruiting them into the growing platelet plug. At the same time, a protein mesh is formed from the plasma protein fibrinogen (not shown). These processes close the gap in the vessel wall, preventing further bleeding until healing can occur.**

been questioned[8]. On the basis of circumstantial evidence, the previously unidentified third ADP receptor was predicted to be coupled to the G_i family of G proteins. It is this protein, now dubbed the $P2Y_{12}$ receptor, that has been identified by Hollopeter *et al.*[1].

The G_i family of G proteins is best known for inhibiting the formation of cyclic AMP (cAMP) by the enzyme adenylyl cyclase. But why do this? The answer lies in the balance needed to maintain platelets in an optimal state of responsiveness. Circulating platelets remain inactive in part because endothelial cells secrete prostacyclin (also known as prostaglandin I_2, PGI_2). This molecule binds and activates receptors on the surface of platelets that stimulate adenylyl cyclase, increasing the formation of cAMP within the platelet. Rising cAMP levels make platelets less responsive to platelet activators. In fact, many such activators — including ADP — work in part by inhibiting adenylyl cyclase and lowering internal levels of cAMP.

The relevance of this effect is shown by the fact that, even before the third ADP receptor was identified, drugs that inhibit the ability of ADP to suppress cAMP formation in platelets were developed and found to block platelet activation. Two of these drugs, clopidogrel and ticlopidine, reduce the risk of recurrent strokes and heart attacks — catastrophic events that involve platelet activation. In the absence of safe and effective oral drugs that prevent platelets from acquiring the ability to stick to each other, ADP-receptor blockers and aspirin (which inhibits the synthesis of prostacyclin and thromboxane A_2, another platelet activator) have been used widely to prevent death and disability from heart attacks and strokes.

Unfortunately, some ADP-receptor blockers have occasionally been associated with the development of a life-threatening syndrome characterized by anaemia, kidney failure and, paradoxically, the blocking of small arteries by clumps of platelets[9]. Until now, the development of successors to these drugs has been slow because the adenylyl cyclase-inhibiting receptor for ADP was not known. The cloning of the gene encoding the $P2Y_{12}$ receptor by Hollopeter *et al.*[1] should help considerably, because it defines a target for drug design.

As well as showing that the $P2Y_{12}$ receptor is present on platelets and can mediate the inhibition of cAMP formation by ADP, Hollopeter *et al.* demonstrate that this protein has the expected pharmacological profile. They also speculate about how a metabolite of clopidogrel might inhibit the receptor, and show that a previously described patient whose platelets fail to respond to ADP lacks a normal form of the gene encoding $P2Y_{12}$. All in all, they make a convincing case that they have indeed identified this biologically and clinically important molecule. ■

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1. Hollopeter, G. *et al. Nature* **409,** 202–207 (2001).
2. Daniel, J. L. *et al. J. Biol. Chem.* **273,** 2024–2029 (1998).
3. Jin, J. G. *et al. J. Biol. Chem.* **273,** 2030–2034 (1998).
4. Cattaneo, M. & Gachet, C. *Arterioscler. Thromb. Vasc. Biol.* **19,** 2281–2285 (1999).
5. Fabre, J. E. *et al. Nature Med.* **5,** 1199–1202 (1999).
6. Léon, C. *et al. J. Clin. Invest.* **104,** 1731–1737 (1999).
7. Offermanns, S. *et al. Nature* **389,** 183–186 (1997).
8. Mahaut-Smith, M. P. *et al. Br. J. Pharmacol.* **131,** 108–114 (2000).
9. Bennett, C. L. *et al. New. Engl. J. Med.* **342,** 1773–1777 (2000).

Climatology

Glacial hiccups

Didier Paillard

The climate instability of glacial times probably resulted from abrupt switches in ocean circulation. A computer-model simulation provides the first glimpse of the dynamics involved.

Twenty years ago, climate was thought to have remained generally stable, at least for the past few millions of years. The belief was that the ocean and the atmosphere adjusted slowly to stately variations in ice-sheet extent during glacial–interglacial cycles. But the study of palaeoclimatic records has since revealed that climate was in fact highly variable during glacial times[1]. It switched abruptly between cold and warm modes, with the temperature in Greenland changing by up to 10 °C in a matter of decades[2]. A crucial step towards understanding these glacial hiccups is presented by Ganopolski and Rahmstorf[3] on page 153 of this issue.

It has long been suspected that ocean circulation in the North Atlantic is involved in the abrupt coolings and warmings during glacial periods[4]. The circulation depends mainly on the density of sea water, which is a function of temperature and salinity. These two properties determine the strength of the so-called thermohaline circulation, which in the North Atlantic contributes to the northwards flow of warm water on the surface, followed by heat release and sinking of the cooler water at high latitudes, with ensuing southerly flow at depth.

As early as 1961 it was proposed[5] that the interplay between the effects of temperature and salinity could lead to different modes of ocean circulation. In particular, changes in the amount of fresh water in the Nordic Seas can affect deep-water formation in the North Atlantic and alter the thermohaline circulation. As shown in Fig. 1a (overleaf), present-day climate corresponds to an active North Atlantic circulation. If freshwater input into the Nordic Seas rises above a threshold value (F_1 in Fig. 1a), the thermohaline circulation must jump abruptly from its equilibrium (warm) branch to a different one. This new branch corresponds to a much reduced circulation, with colder temperatures at high latitude because less heat is transported there.

When the freshwater perturbation vanishes, the Atlantic circulation does not return to its initial behaviour, but stays inactive. Only a negative perturbation (removal of fresh water, for example by evaporation) can bring it back to normal. In other words, the return pathway is not the same as the perturbation one. The system follows a so-called hysteresis loop as shown in Fig. 1a. Model experiments[6,7] have confirmed this behaviour for the Holocene — the interglacial of the past 10,000 years. But palaeoclimatic

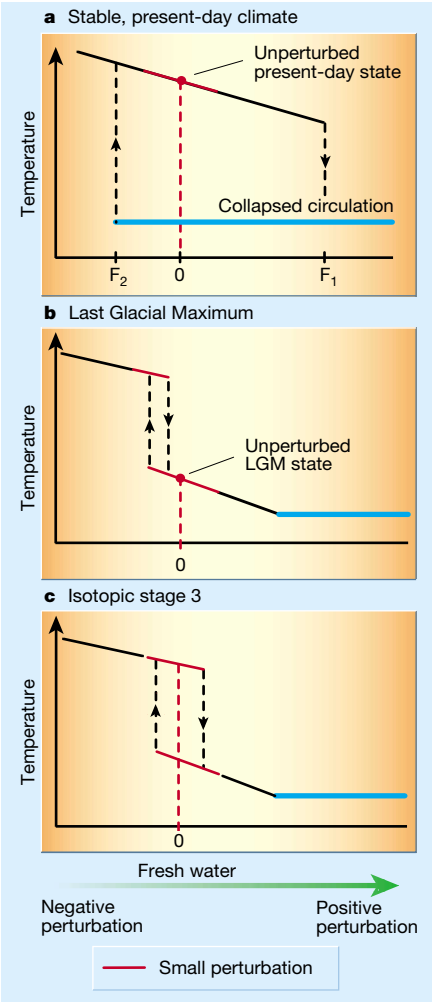

Figure 1 **Climate (temperature) stability as a function of freshwater input at high latitudes in the North Atlantic.** a, **Under present-day conditions, North Atlantic climate has essentially two possible equilibria. When freshwater input exceeds a threshold value F_1, thermohaline circulation jumps from the upper (warm) equilibrium branch to the lower (colder) one, which corresponds to thermohaline collapse (blue line). It can return to the upper branch only if fresh water is removed (by, say, evaporation) and decreases below the threshold value F_2. The hysteresis width F_1–F_2 is large. So present climate is not destabilized by weak freshwater perturbations.** b, **Under the conditions of the Last Glacial Maximum, the hysteresis is much narrower and so the system is much more sensitive to the input or removal of fresh water — even a slight reduction can induce abrupt warmings, and such Dansgaard–Oeschger warming events are evident in the palaeoclimate record. Large inputs of fresh water, as during Heinrich events (ice-sheet melting), will induce a relatively small cooling through thermohaline collapse.** c, **A guess at an intermediate situation, as pertained during isotopic stage 3, around 50,000–30,000 years ago. The warm (upper) branch is more stable than it is under LGM conditions, corresponding to the longer Dansgaard–Oeschger events that occurred at this time.**

records[1] show that the Holocene has been a time of essentially stable climate.

So how do we investigate the large variabilities of glacial times? A prerequisite is a reasonable computer representation of climate at the Last Glacial Maximum (LGM), which occurred around 22,000–19,000 years ago. This is a tough task for the general-circulation coupled ocean–atmosphere models of today's climate; indeed, equilibrating such models for the very different LGM climatic regime is daunting in itself. But a faster track is possible, and a few years ago Ganopolski *et al.*[8] built an 'Earth model of intermediate complexity' that can perform integrations over thousands of years, yet can also represent the main characteristics of the ocean and atmosphere fairly well. The model's relevance was shown when its results for the LGM climate compared favourably with palaeoclimate reconstructions.

In their new paper[3], Ganopolski and Rahmstorf use an improved version of this model to describe the sensitivity of glacial climate to small changes in the amount of fresh water in the Nordic seas. The most notable result is the very different shape of the hysteresis curve under LGM conditions (Fig. 1b). The hysteresis is wide for present-day climate, and can account for the stability of the Holocene because only large freshwater perturbations can destabilize the system. But under LGM conditions, this hysteresis is much narrower, bringing the thresholds for abrupt change closer to the 'unperturbed state'. This explains why glacial climate was so unstable. The LGM equilibrium is located to the right of this hysteresis loop: so even a small loss of fresh water (through increased evaporation, decreased precipitation or run-off from land) induces an abrupt warming, as manifest in the events, known as Dansgaard–Oeschger warmings, recorded in ice cores[1].

The LGM equilibrium is stable if only small amounts of fresh water are added. But, in contrast to the situation today, the lower branch of the LGM hysteresis is not flat. It does not initially correspond to a collapse of the thermohaline circulation, but only to a colder climatic regime where deep-water formation takes place south of Iceland instead of in the Nordic seas. Consequently, there is room for additional cooling through complete thermohaline collapse if there is a substantial addition of fresh water. This is what happened during so-called Heinrich events in the North Atlantic[9] — times, as reflected in sediment cores, when there was large-scale release, and subsequent melting, of icebergs from the polar ice sheets.

But we also need to simulate these rapid warming and cooling events under different external 'forcings'. To start with, we can make a guess for conditions intermediate between a full glacial and a full interglacial (that is, between Fig. 1a and Fig. 1b). Figure 1c shows my own guess for such an intermediate period, 'isotopic stage 3' (50,000–30,000 years ago). Here the hysteresis is wider than in LGM conditions and, like today, the unperturbed state lies inside the hysteresis loop. Warm modes would last longer, as is evident in certain Dansgaard–Oeschger events during this time. So the dynamical picture provided by Ganopolski and Rahmstorf[3] nicely accounts for the phenomenon of glacial variability. The temporal and geographical patterns of events that emerge from the model, in particular the phase relationship between warmings in Greenland and Antarctica, also compare rather well with the palaeoclimatic data[10].

Plenty of questions remain, of course, most notably that concerning the initial causes of the instabilities. Ganopolski and Rahmstorf carefully avoid the problem by applying a weak, but unexplained, periodic forcing to generate Dansgaard–Oeschger oscillations in the model. They mention solar variability as a possible cause. But little is known of such variability, and invoking it is more pulling out a wild card than providing a solid explanation. The thermal response of the climate model (about 7 °C warming over Greenland) is also weaker than ice-core records indicate (about 10 °C). So other feedbacks probably need to be taken into account — changes in the concentration of atmospheric methane[10], for instance. More broadly, the next step in this line of research will require the coupling of climate models with an ice-sheet model that can simulate the storage and release of large amounts of fresh water over centuries or millennia.

The topic of climate stability is high on both scientific and political agendas, and looks set to stay there. A faithful representation of the Earth system in computer-model form is needed to clarify events of the past, better to predict the future. But the route to that end still lies mostly ahead of us. ■

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1. Dansgaard, W. *et al. Nature* **364,** 218–220 (1993).
2. Severinghaus, J. P. *et al. Nature* **391,** 141–146 (1998).
3. Ganopolski, A. & Rahmstorf, S. *Nature* **409,** 153–158 (2001).
4. Broecker, W. S., Peteet, D. M. & Rind, D. *Nature* **315,** 21–26 (1985).
5. Stommel, H. M. *Tellus* **13,** 224–230 (1961).
6. Stocker, T. F. & Wright, D. G. *Nature* **351,** 729–732 (1991).
7. Manabe, S. & Stouffer, R. J. *Nature* **378,** 165–167 (1995).
8. Ganopolski, A. *et al. Nature* **391,** 351–356 (1998).
9. Paillard, D. & Cortijo, E. *Paleoceanography* **14,** 716–724 (1999).
10. Blunier, T. *et al. Nature* **394,** 739–743 (1998).

Daedalus

David Jones

David Jones, author of the Daedalus column, is indisposed.