process that mimics cell differentiation. To do this, they designed synNotch circuits to emulate one feature of the native Delta–Notch system known as lateral inhibition, in which Notch, when activated by Delta from a neighbouring cell, inhibits the expression of Delta in the receiving cell. This signalling produces a chequerboard pattern of two distinct cell populations, one expressing Notch, the other Delta, from an initially uniform population.

In the authors' lateral-inhibition circuit, one of these cell populations produced a green fluorescent protein, the other red. In addition, the two effector domains also promoted the production of different levels of the protein E-cadherin. In this way, the group was able to generate a structure that had rings of colour starting from a single uniform cell population.

With this work, Toda *et al.* have shown how we can design developmental programs to make new living shapes. Of course, there are limits to this approach. The authors' biggest structures are only a few hundred micrometres across, and adhesion-driven self-organization alone is unlikely to generate structures of the size or complexity of organs. But advances in other types of synthetic-biology shape control could help to fill in some of the gaps. For instance, cells have been generated that can be artificially polarized such that asymmetric cell–cell contacts can be made[7], and synthetic circuits have been designed to modify the behaviour of bacteria so that, across a whole population, arrangements are formed that resemble Turing patterns[8]. These patterns — such as stripes, spirals or the spots on a giraffe — arise during development as a result of biological signalling programs.

In the future, the toolkit established by Toda *et al.* could be expanded to generate short- and long-distance cell–cell communication alongside a synthetic system that controls all of the shape-changing operations involved in making biological structures. This could eventually give engineers total control when designing shapes that have some of the properties of living multicellular organisms. Such a development would be a huge advance. Not only could we map the rules of developmental biology by establishing the limits and constraints of shape-changing biological operations, but we could also grow replacement organs and make adaptive living materials — for example, buildings that could construct and heal themselves. ■

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1. Toda, S., Blauch, L. R., Tang, S. K. Y., Morsut, L. & Lim, W. A. *Science* **27**, eaat0271 (2018).
2. Davies, J. A. *J. Anat.* **212**, 707–719 (2008).
3. Morsut, L. *et al. Cell* **164**, 780–791 (2016).
4. Halbleib, J. M. & Nelson, W. J. *Genes Dev.* **20**, 3199–3214 (2006).
5. Nose, A., Nagafuchi, A. & Takeichi, M. *Cell* **54**, 993–1001 (1988).
6. Cachat, E. *et al. Sci. Rep.* **6**, 20664 (2016).
7. Loza, O. *et al. eLife* **6**, e24820 (2017).
8. Karig, D. *et al. Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1720770115 (2018).

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PALAEOCLIMATE

Hosing the North Pacific Ocean

Climate anomalies punctuated the last ice age, characterized by the discharge of icebergs that released fresh water into the North Atlantic Ocean. It now emerges that fresh water also sometimes flooded the North Pacific. SEE LETTER P.241

KAUSTUBH THIRUMALAI

Abrupt cold snaps known as Heinrich events occurred during past ice ages[1]. These millennial-scale periods of colder climate were associated with massive influxes of fresh water to the North Atlantic Ocean. The influxes were caused by discharge of icebergs from the Laurentide Ice Sheet — an immense sheet of ice that covered most of central and eastern North America during glacial epochs (Fig. 1). Studies of such events are of great interest because they could help to indicate whether rapid reorganizations of ocean circulation might occur in the future, and how they might affect climate[2]. On page 241, Maier *et al.*[3] investigate how Heinrich events affected the North Pacific region during the last glaciation (roughly 115,000 to 12,000 years ago), and the influence of the Cordilleran Ice Sheet, North America's western counterpart of the Laurentide Ice Sheet. They report links between changes in ocean circulation in the North Atlantic and melting of the Cordilleran Ice Sheet.

There is abundant evidence that fleets of icebergs episodically surged into the North Atlantic during the last glaciation. Heinrich events were initially identified from the coarse, ice-rafted detritus that forms layers in marine sediments[1]. Numerous palaeoclimate records have since been obtained showing that ocean cooling and freshening (freshwater influx) occurred across the North Atlantic during Heinrich events[4]. The subsequent alteration of the Atlantic Ocean's circulation weakened heat transport between the hemispheres, and is hypothesized to have induced global temperature and precipitation anomalies through both atmospheric and oceanic pathways[5].

It has been more challenging to find evidence that meltwater from the break-up of the Cordilleran Ice Sheet freshened the North Pacific Ocean. Near-coastal sediments in the northeast Pacific reveal that large abundances of freshwater biota were transported to the region by glacial-era meltwater[6], and glacial debris has been uncovered in the region that can be associated with some Heinrich events[7]. By contrast, studies[8] of planktic foraminifera (microscopic plankton that have shells made from calcium carbonate) preserved in sediments from the North Pacific indicate that no changes in salinity occurred during North Atlantic Heinrich events, muddying the picture of how the Cordilleran Ice Sheet affected ocean dynamics and climate during these events.

Maier *et al.* now report a study of marine diatoms — single-celled plankton that have

MAP SOURCE: ILLINOIS STATE GEOLOGICAL SURVEY

Figure 1 | Ancient ice sheets. During the last ice age, North America was covered by a complex of ice sheets, including the Laurentide Ice Sheet over the centre and east, and the Cordilleran Ice Sheet across the west; this map shows the maximum extent of the ice. Maier *et al.*[3] analysed oxygen isotopes in the remains of organisms called diatoms trapped in sediments taken from the North Pacific Ocean (the star indicates the location of the sediment core studied). The changing ratio of isotopes in different layers of sediment reflects changes in the salinity of the sea water in which the diatoms lived. The isotopic measurements reveal that fresh water inundated the North Pacific during certain Heinrich events — millennial-scale periods during which the climate was anomalously cold. The authors conclude that the fresh water came from melting of the Cordilleran Ice Sheet.

shells made from silica — preserved in open-ocean sediments from the northeastern North Pacific (Fig. 1). The authors measured the ratios of stable oxygen isotopes in the diatoms. These ratios reflect past changes in the temperature and isotopic composition of sea water, which, in turn, vary with changes in global sea level and local salinity. The same principle was used in earlier studies[8] of planktic foraminifera, but diatoms can thrive in colder and less saline environments[9] than can many planktic foraminiferal species. Maier and colleagues' measurements reveal that large and abrupt intrusions of low-salinity waters occurred at their study site, coinciding with the timing of some Heinrich events. The authors interpreted these intrusions as evidence of meltwater originating from the Cordilleran Ice Sheet.

The researchers went on to carry out a series of computational climate-modelling experiments, of a type known as hosing experiments. Such simulations are used to study anomalies in global climate and ocean circulation that arise in response to abrupt climate change, and involve artificially introducing fresh water into the oceans at high latitudes, typically routed to the North Atlantic[5]. Maier *et al.* extended the hosing approach in two ways. First, they used a climate model that represents isotopic tracers, which thus enabled a more direct comparison of the simulations with their measurements. And second, they performed two sets of simulations, one in which only the North Atlantic was hosed, and the other in which both the North Atlantic and North Pacific were hosed.

The authors found that the simulation in which freshwater input was confined to the North Atlantic did not indicate that low-salinity waters entered the North Pacific Ocean, contradicting the findings from their diatom measurements. Despite this difference, the simulation did reproduce the ocean–atmosphere dynamics thought to have occurred across the Pacific in response to perturbations in the North Atlantic[5]. It also revealed poleward routing of warm, subtropical ocean waters due to shifts in tropical rainfall. Maier *et al.* therefore propose that the rerouted warm waters might have been responsible for the melting of parts of the Cordilleran Ice Sheet, adding fresh water to the North Pacific — a scenario that they could model by hosing the North Pacific as well as the North Atlantic.

Indeed, when the authors simulated this scenario, it provided a better match to the diatom observations. Moreover, the simulation suggests that salinity changed only negligibly at depth in the North Pacific. This might explain why no change in salinity was recorded in the isotopic study of foraminifera — it is thought that these organisms do not dwell at the topmost part of the ocean in this region. However, the diatom data indicate that freshwater influxes to the North Pacific did not occur during every Heinrich event. This could be because all Heinrich events are not created equally[1,4]. Sure enough, when Maier and colleagues performed additional simulations of North Atlantic perturbations involving exceptionally cool background temperatures, they found that the conditions produced were not conducive to melting of the Cordilleran Ice Sheet.

The new study is a major advance in our understanding of freshwater events in the North Pacific, but questions remain owing to the limitations of the time resolution of the sediments in the core that was analysed, and because the low abundance of diatoms in some sedimentary layers prevented the authors from carrying out their analysis for the corresponding periods of geological time. For example, the lack of evidence of freshwater pulses in proxies of the North Pacific surface ocean during some Heinrich events is puzzling, given the presence of glacial detritus. Furthermore, we still do not know how stable the Cordilleran Ice Sheet would be in response to shifts in Pacific climate that are unrelated to Heinrich events.

Importantly, further research is required to determine whether Cordilleran-meltwater events influenced circulation in the Pacific, or even in the Atlantic. More broadly, a more-refined understanding of Cordilleran-meltwater pulses and the associated effects on regional temperature and precipitation will benefit our theories of abrupt climate change. ■

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1. Heinrich, H. *Quat. Res.* **29**, 142–152 (1988).
2. Liu, W., Xie, S.-P., Liu, Z. & Zhu, J. *Sci. Adv.* **3**, e1601666 (2017).
3. Maier, E. *et al. Nature* **559**, 241–245 (2018).
4. Hemming, S. R. *Rev. Geophys.* **42**, RG000128 (2004).
5. Okumura, Y. M., Deser, C., Hu, A., Timmermann, A. & Xie, S.-P. *J. Clim.* **22**, 1424–1445 (2009).
6. Lopes, C. & Mix, A. C. *Geology* **37**, 79–82 (2009).
7. Hendy, I. L. & Cosma, T. *Paleoceanography* **23**, PA2101 (2008).
8. Maier, E. *et al. Paleoceanography* **30**, 949–968 (2015).
9. Harrison, P. J. *et al. Prog. Oceanogr.* **43**, 205–234 (1999).

DNA DAMAGE

Breaking the replication speed limit

Inhibitors of PARP proteins are used in cancer treatment. It emerges that PARP inhibitors exert their effect by accelerating DNA replication to a speed at which DNA damage occurs. SEE LETTER P.279

ANNABEL QUINET & ALESSANDRO VINDIGNI

The two strands of DNA's double helix unwind to be copied, with a structure called a replication fork forming at the point of separation. The speed at which the replication fork progresses along DNA — and so the speed of replication — must be controlled to guarantee faithful duplication of the genome. On page 279, Maya-Mendoza *et al.*[1] define a molecular network involved in the regulation of replication-fork speed. Changes to this network can cause that speed to increase above a safe threshold, causing DNA damage and genomic instability.

Replication forks that encounter damage in the genome sometimes temporarily stop, allowing DNA repair to occur before replication continues. Proteins of the poly(ADP) ribose polymerase (PARP) family, particularly PARP1, assist in the repair of breaks in single strands of DNA through a process called PARylation[2], in which the proteins synthesize chains of ADP-ribose molecules that attract repair proteins to the damaged DNA. PARP inhibitors — drugs that block the PARylation activity of PARP proteins — are showing promise as therapeutics to treat various cancer types[3]. Previous models have proposed that, by preventing PARP activity, PARP inhibitors cause replication forks to stall for abnormally long periods, and eventually to collapse, when they encounter DNA damage[4]. This leads to accumulation of DNA damage owing to improper replication and death of the treated cells[4].

Maya-Mendoza *et al.* challenge the idea that PARP inhibitors perturb the ability of replication forks to progress. The authors found that treating proliferating human cells with the PARP inhibitor olaparib *in vitro* led to aberrant acceleration of fork speed. They provide evidence that, if fork speed increases above a threshold speed of 40% faster than normal, there is insufficient time for the forks to recognize damaged DNA in need of repair. This leads to accumulation of DNA damage and reduced cell viability. Supporting this idea, the authors found that violation of the threshold speed led to the activation of proteins involved in a DNA-damage response, although the mechanism by which this occurs needs to be further investigated.

To uncover the pathway by which PARP