factor productivity for agriculture by around 21% since 1961.

Although crop yields are determined by the cumulative result of daily weather conditions over the course of a growing season, a few shocks such as floods or droughts at crucial growth stages can cause severe damage or total loss, affecting gross agricultural productivity. All of these factors suggest that the agricultural sector is vulnerable to extreme rainfall. The fact that Kotz and colleagues estimate the climate dependence of the agricultural sector to be lower than expected might indicate the need for new measures of climate. Improved metrics might capture, for example, an awareness of the importance of growth stages, or consideration of irrigation and other factors that partly mitigate the negative effects of deficient rainfall and high temperature extremes. Land drainage could be another factor that complicates the impact of excessive rainfall.

The causal mechanisms behind these statistical relationships are yet to be determined. Kotz *et al*. defined extreme daily rainfall as the annual sum of rainfall on days exceeding the 99.9th percentile of the distribution spanning 1979 to 2019. This amounts to counting only the rain that fell on the rainiest of 1,000 days. How do these rare and local events cause substantial economic shocks and cascade into long-term effects across all sectors at regional, national and global scales? Is it because they are linked in time and space and, together with other climatic anomalies, produce persistent and widespread impacts on economic activities?

The 2021 floods in Europe and China occurred at around the same time, and it is tempting to assume they were connected. But what about the snow, sleet and freezing rain that accompanied low-temperature extremes five months earlier in Texas? These compound effects resulted in a massive power failure, leaving more than 4.5 million homes and businesses without electricity. In fact, extreme rainfall events are linked through complex networks of global climatic patterns[7], and might also be related to heatwaves, cold surges, droughts, storms and other weather extremes. The integrated result of these compounded factors could lead to substantial economic impacts worldwide. Rainfall extremes might also be related to worldwide economic changes through the globalization of trade — a natural disaster in one location can affect the economy of another if their economies are interdependent. These mechanisms could change local impacts of climate extremes into indirect positive or negative economic effects elsewhere.

The frequency and intensity of precipitation extremes have been increasing in recent decades, and this trend is projected to continue with global warming[8]. In attempting to forecast the impact of these increases, a major problem is that most climate models underestimate extreme precipitation, and so projections are associated with large uncertainties. Such models therefore provide unreliable estimates of the economic effect of events resulting from excessive rainfall. With the help of numerical modelling and machine-learning techniques, further research might uncover the physical mechanisms behind the increase in precipitation extremes, and offer ways to mitigate them[9]. Until then, improved understanding of the uncertainties associated with climate models will enable policymakers to estimate rainfall extremes more accurately and to manage the related economic risks more effectively.

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Biochemistry

Structures show how salt gets a sweet ride

David Drew

Proteins spanning the membranes of cells of the intestine and kidney use sodium-ion gradients to take up glucose, enabling water absorption, too. The structures of these transporter proteins have now been observed in detail. **See p.274 & p.280**

I was close — oh, so close — when I collapsed just outside the stadium with less than one kilometre of the marathon to go. As a biochemistry student, I should have known better, but I had made the mistake of selecting water instead of the electrolyte drinks offered, and so ended up inside an ambulance dehydrated and embarrassed. The discovery that the transport of glucose and sodium ions from the digestive tract into the body is coupled and facilitates the absorption of water was a breakthrough of the twentieth century[1]. A simple salt–glucose mixture has since saved millions of lives, and kept runners from collapsing — well, mostly. Now Han *et al.*[2] (page 274) and Niu *et al.*[3] (page 280) present structures of the membrane-spanning transporter proteins that carry sodium and glucose across cell membranes in humans.

The protein known as sodium-coupled glucose cotransporter 1 (SGLT1) was first shown[4,5] in the 1980s to be responsible for the active transport of glucose across the brush-border membrane that lines the small intestine. The movement of sodium ions down their concentration gradient (from where they are highly concentrated to where they are less concentrated) enables SGLT1 to transport glucose into cells against its concentration gradient, in contrast to other glucose transporters (called GLUTs) that shuttle the sugar passively into the bloodstream[6,7]. SGLT1 also carries water along for the ride — in total, roughly 5 litres a day for an adult human — and thus is essential for oral rehydration therapy[6,8].

A closely related protein called SGLT2 works with SGLT1 in the kidney to reabsorb about 99% of the glucose that the kidney filters out of the blood, to prevent this glucose from being excreted in the urine[7]. Several SGLT2 inhibitors have been approved as drugs to lower blood glucose levels in individuals with type 2 diabetes[7]. Although the structures and computational modelling of a bacterial SGLT (vSGLT) have provided an overall framework for the transport mechanism[6], the structures of the transporters in humans needed to be defined for researchers to fully understand how they act in people and how they can be selectively inhibited by drugs.

The structures of human SGLT1 and SGLT2 were resolved using a technique called

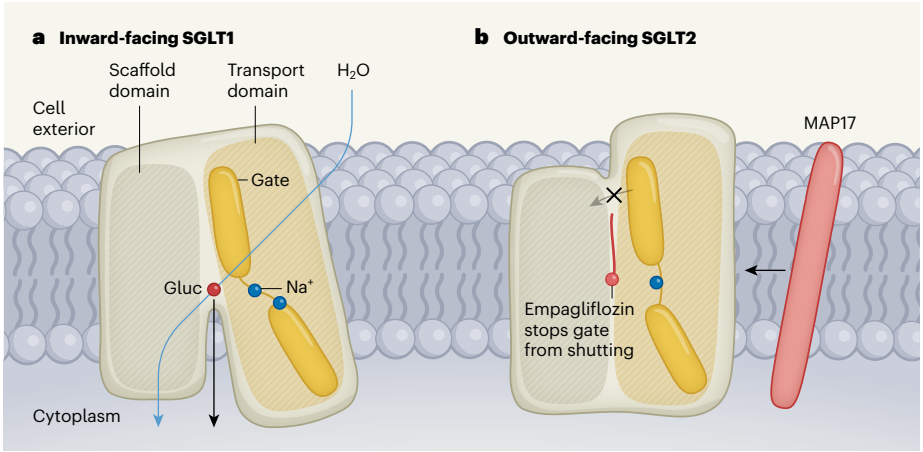

Figure 1 | Transporter proteins that move salt, sugar and water across cell membranes. a, The membrane-spanning protein SGLT1 couples the transport of two sodium ions (Na^+) and a glucose sugar molecule (Gluc) into cells of the intestine and kidney. This transport also facilitates the movement of water (H_2O) into the cell. SGLT1 contains two structural domains, known as the scaffold domain and the transport domain. Han *et al.*[2] resolved the structure of human SGLT1 with the transport domain oriented against the scaffold domain such that a cavity was open towards the inside of the cell (inward-facing state), and mapped the likely route by which water enters the cell. Gates represent the two half-helices TM1a-b and TM6a-b. **b**, Niu *et al.*[3] determined the structure of a related transporter, SGLT2, which transports one sodium ion for every glucose molecule absorbed. The authors resolved the structure of human SGLT2 in its outward-facing state in complex with a protein called MAP17 (which interacts with a peripheral helix in the transport domain of SGLT2), and bound by a drug called empagliflozin. The drug stops the outside-gate portion of the transporter from shutting, thereby halting the protein's transition to the inward-facing state.

cryo-electron microscopy. Because they are relatively small proteins, they needed to be made larger, as well as more rigid, for this procedure. Han *et al.* generated SGLT1 variants that had specific changes to the amino-acid sequence to stabilize the protein, and attached an antibody molecule to reduce the protein's flexibility and to facilitate the alignment of images of the protein particles. Niu *et al.* replaced a flexible loop in SGLT2 with green fluorescent protein (GFP). They then tethered an antibody that binds to GFP to a membrane-spanning protein called MAP17, which associates with SGLT2 to enhance the transporter's activity[9].

Han *et al.* found that, although SGLT1 includes an extracellular 'lid' domain not present in vSGLT, its overall architecture is much like that of the bacterial transporter[6,10]. Indeed, nature has a habit of sticking with a winning formula: both SGLT1 and SGLT2 adopt what is known as a LeuT-fold structure[6,10]. The LeuT-fold is so named because it was first described for the structure of a transporter protein that couples sodium transport with that of the amino acid leucine, but it has since been observed in many other transporter families[6,11].

The LeuT-fold is defined by two main structural regions — a 'scaffold' domain and a 'transport' domain. LeuT-fold transporters operate according to the 'rocking-bundle' alternating-access mechanism[11]. In brief, after sodium has bound the protein in its outward-facing state, its interaction with the sugar molecule lying between the two main domains catalyses the rearrangement of the transport domain so that it moves against the scaffold, thereby exposing the sugar and sodium to the inside of the cell[6,11]. The transport domain contains two unwound helices (TM1a-b and TM6a-b) that act as gates in the transport mechanism. Only when the sodium and the glucose molecule are bound do these helices move inwards to close access to the sugar-binding site from the outside; when the cavity of the protein faces the inside, the gating helices move outwards again to enable the release of sodium and glucose[6,11]. Han *et al.* determined the structure of SGLT1 in its inward-facing state, whereas Niu *et al.* resolved the structure of SGLT2 in its outward-facing state (Fig. 1).

SGLT1 can transport glucose or another type of sugar called galactose, whereas vSGLT transports only galactose[6]. To understand this difference, Han *et al.* compared the SGLT1 structure with the previously reported[10] galactose-bound structure of vSGLT. They found that a single substitution of one of the amino-acid residues in SGLT1 abolished its ability to bind to glucose, highlighting how finely tuned the transporter's selectivity for sugar is.

Han *et al.* also determined the structure of SMCT1, a more distant family member of the SGLT transporters that, instead of sugar, transports monocarboxylate molecules[12]. The authors resolved its structure in complex with one such monocarboxylate (butyrate), demonstrating how the shape and chemistry of the binding site of this family of transporters are modified to accommodate non-sugar substrates.

It has not been clear how SGLT1 can carry water across the membrane. Using computational simulations, Han *et al.* identified a water-filled passageway through the SGLT1 structure, and showed that SGLT1 variants with substitutions of amino-acid residues along this route transport less water than does wild-type SGLT1. Although the identification of this waterway is exciting, future experiments are required to tease out why water flows through SGLT1 only when the transporter is active[6,8].

Compounds that have been developed to inhibit SGLT2 bind preferentially to the transporter in its outward-facing state, and are similar to a plant molecule called phlorizin, which comprises a sugar group attached to a molecular 'tail' (an aromatic aglycone)[7]. Niu and colleagues' structure of SGLT2 in complex with the inhibitor empagliflozin, a diabetes drug, reveals how the sugar part of the molecule is coordinated in a similar way to galactose in vSGLT[10], but with the aglycone tail extending towards and interacting with the extracellular TM1b and TM6a gates. The SGLT2 inhibitor elegantly blocks the gates from shutting and thus halts transport. Niu and co-workers' biochemical assays confirmed that the binding preference of empagliflozin for SGLT2 over SGLT1 was due to a few amino-acid-residue differences in the extracellular gate compared with SGLT1.

The SGLT2 structure should help to guide the development of inhibitors that are more specific for SGLT2, as well as those that more broadly block both SGLT1 and SGLT2. Intriguingly, Niu *et al.* show that the way in which empagliflozin inhibits SGLT2 resembles the way antidepressant drugs inhibit another LeuT-fold transporter called SERT, which uses sodium to transport the neurotransmitter molecule serotonin into neuronal cells in the brain[13]. Targeting gating regions might prove to be a fruitful strategy for developing drugs that act on other small-molecule transporters.

The SGLT structures in their outward- and inward-facing states provide much-needed details with which to unravel how these transporters operate. Nevertheless, the structures of other states — for example, those with gates fully opened and closed — and an understanding of how all the states are dynamically connected, are needed, too. In reality, transport is an intricate process involving finely coupled interactions, and single amino-acid perturbations can have dramatic consequences. Indeed, Niu *et al.* mapped the effects of mutations of the gene encoding SGLT1 that cause the inherited metabolic disorder galactose–glucose malabsorption (GGM)[6], and found that the changes in amino-acid sequence caused by these mutations are distributed across the entire SGLT1 protein.

The composition of the membrane itself, and possibly the composition of other membrane proteins, are also known to influence

the conformational preferences and dynamics of transporters. Han *et al.* found that a cholesterol-based molecule could bind to SGLT1, and Niu *et al.* observed the interaction of the protein MAP17 with one of the helices in SGLT2, providing a starting point for addressing how the transporters might be regulated by other factors.

Finally, one sodium ion is absorbed for every glucose molecule in SGLT2, whereas in SGLT1 two sodium ions are absorbed[6]. Although the structures described by Han *et al.* and by Niu *et al.* pinpoint the sodium binding sites, a better dissection is needed of exactly how sodium-ion and sugar binding are intimately coupled to enable these differences. And with that, a new marathon begins.

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Biogeochemistry

A microbe that uses crude oil to make methane

Guillaume Borrel

A microorganism that dwells in an underground oil reservoir has been found to degrade various petroleum compounds and use them to produce methane through a previously unreported biochemical pathway. **See p.257**

Microbial communities tend to use the most energy-rich and most easily metabolized compounds that they have at their disposal. This leads to a progressive enrichment of compounds that are difficult to break down and that provide little energy, particularly in the absence of oxygen or other inorganic electron acceptors. Under these conditions, the use of hydrocarbons — molecules consisting of carbon and hydrogen, such as alkanes — has been thought to rely entirely on a collaboration (known as syntrophy) between bacteria that break down these compounds into acetate and molecular hydrogen (H_2), and microorganisms called methanogenic archaea that use the molecules to produce methane (CH_4), the simplest hydrocarbon[1–3]. On page 257, Zhou *et al.*[4] overturn this long-standing account of a division of labour in the methanogenic degradation of hydrocarbons by reporting that a single type of microorganism can degrade various large hydrocarbons into methane (Fig. 1).

Whereas many microorganisms can use a large range of substrates to obtain energy, methanogenic microorganisms (methanogens) are highly specialized. Most of them can obtain energy only by reducing carbon dioxide into methane using molecular hydrogen as an electron donor, and a few others can use acetate and methylated compounds (such as methanol and methylamines). Over the past five years, genomics studies have described several lineages of previously unknown and not-yet-cultured methanogenic microbes from various oxygen-free environments, including marine sediments, hot springs and subsurface oil reservoirs[5–8].

> **"The findings shed light on a previously unappreciated source of methane production."**

Although most of these newly discovered methanogens were inferred also to rely on simple compounds, mainly methylated compounds reduced by hydrogen[5,9], a great surprise was the prediction of a previously undescribed pathway for generating methane from multi-carbon alkanes and, possibly, long-chain fatty acids[5,10]. This metabolic pathway was initially predicted from genomes belonging to a class of uncultured archaea named *Candidatus* Methanoliparia[5], because members of this class mostly occur in oil reservoirs or environments contaminated with petroleum.

Zhou *et al.* collected crude oil from Shengli oilfield (northeast China), and found that *Ca.* Methanoliparia represented about half of the archaeal community in these samples. When the samples were incubated at between 35 °C and 65 °C, without oxygen or other inorganic electron acceptors, long-chain alkanes (linear chains of 13–38 carbons) were completely depleted, and a large amount of methane was produced. The authors similarly observed reductions in the levels of hydrocarbon molecules composed of a carbon ring bound to a long-chain alkyl group.

Because *Ca.* Methanoliparia are far from being the only microorganisms in these cultures, one might ask at this stage whether the production of methane from petroleum compounds might have resulted from the activity of conventional bacteria–archaea associations. Indeed, bacteria known to break down hydrocarbons were present, even if they represented only 4% of the total microbial community in the original culture. However, after several transfers of the culture into fresh medium, interspersed by weeks of incubation, the proportion of these bacteria dropped to less than 0.1%. By contrast, the abundance of *Ca.* Methanoliparia (around 40% of the microbial community) and the rate of methanogenic degradation of long-chain alkanes was maintained over these transfers.

Further supporting the absence of syntrophic associations involving *Ca.* Methanoliparia, Zhou *et al.* used microscopy to reveal that these archaea generally occurred alone and not in aggregates of multiple species (as had been shown previously[10]). Moreover, *Ca.* Methanoliparia genomes lack genes encoding enzymes and nanowire structures that are involved in electron transfer between syntrophic partners[5,10], corroborating the idea that *Ca.* Methanoliparia work alone. In *Ca.* Methanoliparia, as in the syntrophic partnerships between alkane-oxidizing bacteria and methanogenic archaea, electrons released by the alkane-oxidation pathway are used by the methanogenesis pathway. But, in *Ca.* Methanoliparia, the two pathways occur within one cell.

The predicted metabolic route for methanogenic degradation of long-chain hydrocarbons by *Ca.* Methanoliparia involves a combination of enzymes that are otherwise partitioned between syntrophic archaea and bacteria, as well as enzymes specific to *Ca.* Methanoliparia (Fig. 1). Among the enzymes that are used both in the *Ca.* Methanoliparia route and in the route mediated by syntrophic archaea and bacteria is the methyl-coenzyme M reductase