waters from different parts of the lake are mixed. This ratio thus quantifies the effective moisture or hydroclimate indirectly, as long as there are sufficient quantities of both types of GDGT to obtain robust ratios. Branched GDGTs can also act as a 'palaeothermometer' – past abundances of this type can be compared with modern measurements as a proxy for temperature, although the season in which the compounds were produced is difficult to pinpoint, as is the actual temperature[8], so this method tracks only relative changes.

Baxter and colleagues present a reconstruction that couples extraordinarily high-resolution temperature and hydroclimate data and is derived from GDGTs from Lake Chala, a crater lake straddling the border between Kenya and Tanzania. An international drilling operation, DeepCHALLA, extracted a long core from the lake, containing sediment deposited during the transition from the most recent glacial period to the current interglacial period, which started 11,700 years ago. The core is presumed to contain annual laminations, small sequences of fine layers deposited each year, that date back thousands of years – a rare acquisition in this region, and particularly so in the context of tropical, terrestrial sediment archives, which are notoriously difficult to date.

Equipped with biomarker data of unprecedented resolution, Baxter and colleagues demonstrated that the correlation between temperature and moisture switched from positive to negative at the glacial–interglacial transition, when CO_2 concentrations rose above 250 parts per million (p.p.m.) – well below more modern values of 420 p.p.m. (ref. 9). And by showing that Lake Chala is representative of a larger region, they concluded that these findings hold for the Greater Horn of Africa.

The authors suggest that the hydroclimate was limited by the amount of thermal energy in the climate system during the glacial period, but this relationship changed around the transition to the interglacial period, when the hydroclimate instead became dependent on the amount of moisture in the system. Before the switch, high temperatures generated moisture in the atmosphere, mainly through monsoons. But temperatures in the interglacial period have peaked at levels higher than those of the glacial period; above a certain threshold, these high temperatures compromise the supply of moisture and inhibit precipitation. The change therefore shifted the warm-makes-wet paradigm to a warm-makes-dry paradigm.

There is much debate about how eastern African palaeoclimatology is affected by external factors, including low-latitude solar radiation; nearby sea surface temperatures and gradients; and high-latitude-driven processes, such as oceanic circulation and the waxing and waning of ice sheets in the Northern Hemisphere. For example, Baxter and colleagues uncovered droughts in eastern Africa during the glacial period that coincided with large groups of icebergs moving into the North Atlantic Ocean. The authors suggest that the droughts might have been caused by reduced Indian Ocean sea surface temperatures associated with the ice events.

However, other records[10] from the Pleistocene era (from 2.6 million to 11,700 years ago) suggest that tropical solar radiation consistently caused variation in the regional monsoonal hydroclimate over longer time periods than those studied by Baxter and co-workers. This implies that droughts might have been caused by external factors further back in the geological record other than North Atlantic ice or associated changes in sea surface temperature. Baxter *et al.* add to growing evidence that the relative impact of these factors on regional hydroclimate can change over time[10]. And, most importantly, they identify mechanisms behind these threshold shifts.

Disentangling the temperature–hydroclimate relationship in eastern Africa helps to reconcile model-based predictions of increased hydrological activity with the intense and frequent droughts that have occurred in the past few centuries. Baxter and colleagues' work suggests that the region will become drier as temperatures increase, because the warmer air will limit the supply of evaporative moisture – a mechanism that will be further enhanced by land–atmosphere feedbacks. It remains unclear, however, why climate models with realistic CO_2 levels, moisture–temperature relationships and landscape features continue to predict increased precipitation and decreased droughts[1]. Perhaps improved modelling is needed to better understand the interaction between the monsoon system and the transport of moisture to and across this varied, tropical region.

Palaeoclimate reconstructions are crucial for understanding future transitions through varying climate conditions[3]. Although Baxter *et al.* posit a straightforward explanation for the paradigm shift that they have uncovered, confidence in this mechanism, and the specific CO_2 threshold that they suggest, would certainly be bolstered by further study into past warm intervals for which there are good CO_2 estimates, such as the Eemian period (between 127,000 and 106,000 years ago). The DeepCHALLA archive could help in this respect, because it offers a window into the climate as early as 250,000 years ago. And as Baxter and colleagues' study shows, the archive promises data of exceptionally high resolution, which can lead to fresh insight into past and future climates.

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Ageing

A molecular driver of cognitive decline

Bart J. L. Eggen

When DNA is misplaced inside cells, the cGAS–STING molecular system triggers inflammation. It emerges that stimulation of this mechanism in microglial cells of the brain during ageing contributes to cognitive decline. **See p.374**

First mentioned in the fifth century BC by the father of history, Herodotus, the water of the mythical fountain of youth is said to restore youthfulness and confer immortality. Clearly, people have long been fascinated by the idea of delaying – or, even better, reversing – ageing. It is safe to say, however, that progress towards this goal has been slow. In the meantime, societies are ageing rapidly: by 2030, one in 6 people will be over 60, and between 2020 and 2050, the number of people over 80 is expected to

triple (see go.nature.com/448ifde). Nevertheless, our understanding of the myriad biological mechanisms that underpin ageing is developing, and, on page 374, Gulen and colleagues[1] pinpoint one molecular pathway that contributes to ageing-related inflammation and neurodegeneration. Notably, inhibiting this pathway in aged mice prevents ageing-associated inflammation, and improves cognitive and motor performance.

At the biological level, ageing is associated with damage to molecules and cells that accumulates over time. This leads to a loss of resilience, which is a major risk factor for many diseases, including neurodegenerative disorders. Indeed, for many diseases of the brain, age is the largest risk factor. This gradual deterioration of molecular, cellular and tissue 'fitness' underlies biological ageing[2].

One of the particular hallmarks of ageing is 'inflammageing'[3], characterized by chronic, low-grade inflammation in the absence of overt infections. In this condition, ageing (senescent) cells secrete molecules that promote inflammation or degrade the extracellular matrix, the network of proteins and molecules that surrounds and supports cells. Inflammation is a normal, physiological response of an organism or tissue to a bacterial or viral infection — but inflammageing is associated with an increased risk of morbidity and mortality.

Previous work identified a system that cells use to sense DNA in the cytosol, namely, the cGAS–STING system (cyclic GMP–AMP synthase stimulator of interferon genesis)[4,5]. In cells, DNA should be located either in the nucleus or in the power-generating organelles, the mitochondria. The presence of DNA in the cytosol is indicative of damage or infection, and a trigger for the cGAS–STING pathway. When this pathway is activated, it induces a particular type of immune response — a type 1 interferon response — that normally protects neighbouring cells from infection. During ageing, however, activation of the pathway is thought to be a key driver of inflammageing, senescence and functional decline.

Gulen *et al.* have now delved further into the role of cGAS–STING in neuroinflammation, neurodegeneration and biological ageing. They have investigated the brains of ageing mice, elucidating the source of the cGAS–STING trigger and the particular cells in which this pathway is activated (Fig. 1). Specifically, the authors find that cytosolic DNA derived from perturbed mitochondria activates the pathway in ageing microglia, the main immune cells in the brain — an observation that agrees with earlier findings that cGAS–STING is involved in activating microglia and in neuroinflammation[6–8].

Microglia account for some 10% of the brain's total cell population[9] and carry out a wide range of functions, including protecting brain tissue against disease-causing microorganisms by killing and devouring them. However, excess activation of microglia has been viewed as potentially detrimental to the brain[9]. Gulen *et al.* find that, in aged mice, it is the cGAS–STING pathway in microglia that is responsible for inducing an inflammatory response, causing damage to neurons (neurotoxicity) and impairing performance in memory tasks.

Inhibiting this pathway in mice with a small-molecule inhibitor, H-151, suppressed the inflammatory properties of senescent cells in many organs, including the brain, and attenuated the ageing-associated decline in cognition and motor performance (endurance). In corroborative experiments, the authors used mice engineered to express a hyperactive cGAS protein specifically in microglia. Neuroinflammation was induced and microglia changed their appearance and expressed interferon genes (through the STING pathway) — an event that could be inhibited with H-151.

"DNA derived from mitochondria activates the pathway in ageing immune cells in the brain."

This study provides key insights into the mechanistic basis of inflammageing in the brain, and a clearer picture of how ageing-associated deterioration of organelle and cell fitness leads to neurodegeneration. Interesting questions for the future include whether a hyperactive cGAS protein might be sufficient to induce the characteristics of premature ageing *in vivo*. Also, Gulen *et al.* focus on mitochondrial DNA as the trigger of the cGAS–STING pathway — but is it the sole trigger? And is the cGAS–STING pathway in microglia activated only from within the cell itself (by the microglia's own mitochondrial DNA), or can nuclear or mitochondrial DNA from other damaged brain cells initiate similar responses? Are other triggers or ageing pathways[2] also in play, or affected by cGAS–STING activation? Is there a causal relationship between cGAS–STING activation and neurodegeneration? Interfering with this pathway in experimental models of neurotoxicity or neuronal loss would shed more light on these relationships.

Furthermore, before even thinking about interfering with the cGAS–STING pathway in humans, detailed and long-term studies of small molecules such as H-151 or similar compounds in other animals are needed. This is because it is crucial to understand whether there are any side effects associated with long-term inhibition of a pathway that is essential to processes such as combating viral infections[4,5].

It will also be important to confirm that the cGAS–STING pathway, its triggers and consequences — identified in mice by Gulen *et al.* — translate to the human brain. Mice live for just 2–2.5 years, whereas people live for an average of 80–85 years and some of our microglia survive for more than 20 years[10]. So the molecular and cellular changes that occur in microglia during ageing might be fundamentally different between people and mice[11]. This molecular pathway does seem to be a key driver of brain ageing, but only time will tell whether inhibiting it will open the way to the fountain of youth.

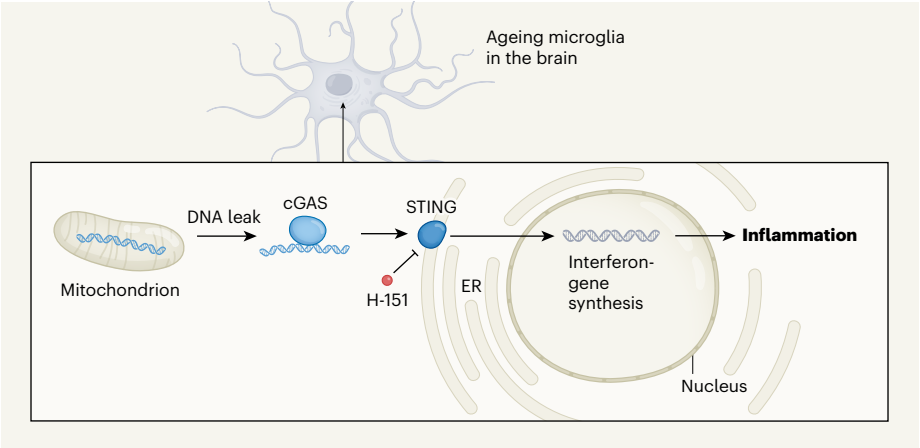

Figure 1 | Inflammageing in the mouse brain. Gulen *et al.*[1] have investigated how ageing-associated inflammation and neurodegeneration are triggered in the brains of mice. The authors find that leakage of DNA from energy-generating organelles (mitochondria) in the brain's main immune cells (microglia) stimulates the cGAS–STING pathway: detection of DNA by the cGAS protein leads to activation of the STING protein in the endoplasmic reticulum (ER, an organelle around the nucleus). This triggers the expression of type 1 interferon genes in the nucleus, causing inflammation and faster ageing. The authors use the small molecule H-151 to inhibit the cGAS–STING pathway in old mice, breaking the cycle of inflammageing and neurodegeneration.

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Mathematics

Shaped to roll along a programmed path

Elisabetta Matsumoto & Henry Segerman

An algorithm has been developed for constructing a 3D shape that follows an infinitely repeating path as it rolls under gravity. The approach could have applications in quantum computing and medical imaging. **See p.310**

A single wheel follows a straight line as it rolls downhill, but can change direction by rotating about its contact point with the ground. Two wheels connected by an axle have much less freedom — with no common point about which to rotate, they are forced to move along parallel straight lines forever. Trains use an ingenious method to solve this problem: their wheels are conical, so the wheel on the outside edge of a turn can keep up with the other wheel by riding the train track at the wide end of the cone. The outside wheel spins at the same rate as the inside wheel, but travels farther (see go.nature.com/3jjykjc). In this way, the track's shape controls the train's path.

On page 310, Sobolev *et al.*[1] have turned this relationship around by designing an object whose path is determined by its own shape, instead of by the shape of the ground. The authors term these objects trajectoids, and then 3D print trajectoids to show that the objects follow a pre-programmed periodic path down a gently sloping plane. In some cases, the paths of these objects match the desired trajectories even when they are made to roll briefly uphill.

To understand how such a shape could be created, imagine rolling a clay ball along a path that has been drawn on a tabletop, flattening a version of the path into the clay (Fig. 1). The shape of the ball now encodes both the trajectory across the table and the way in which the ball must rotate as it moves along the drawn path. But the ball's surface area is limited, so the shape can program tabletop trajectories only up to a certain length. Beyond this point, the ball would stop following the desired path, unless the path on the tabletop repeats itself, as in the case of Sobolev and colleagues' periodic paths.

Trajectoid-like objects have been reported previously, but not with this level of generality — existing attempts have looked at objects that roll along relatively simple repeating paths. One example is the sphericon, a shape that follows a wiggling trajectory, which is encoded in a spherical path that looks similar to the seam of a baseball[2]. Another example was devised by one of us in response to a question a circus performer asked us at a juggling convention: his giant sphericon-like apparatus could zigzag acrobats across a stage, but they would have to stop and go backwards at the edge of the stage[3]. The modified design that enabled the apparatus to turn in a circle is perhaps the previous effort that came closest to Sobolev and colleagues' trajectoids.

Spheres have a peculiar property that makes closing the path of a trajectoid difficult. Imagine that the ball of clay on the table is a globe. The north pole points upwards; Asia is to the left and the Americas to the right. Now imagine rolling it around on the table along any path until the north pole points upwards again. You'll almost certainly find that a different part of Earth faces you. But if a path on this globe is to trace out a repeating path on the table, it must have a special condition: not only does it need to return the north pole to the top, it also needs to align the continents with their initial positions.

Sobolev *et al.* took this idea and devised an algorithm for creating a shape that follows the

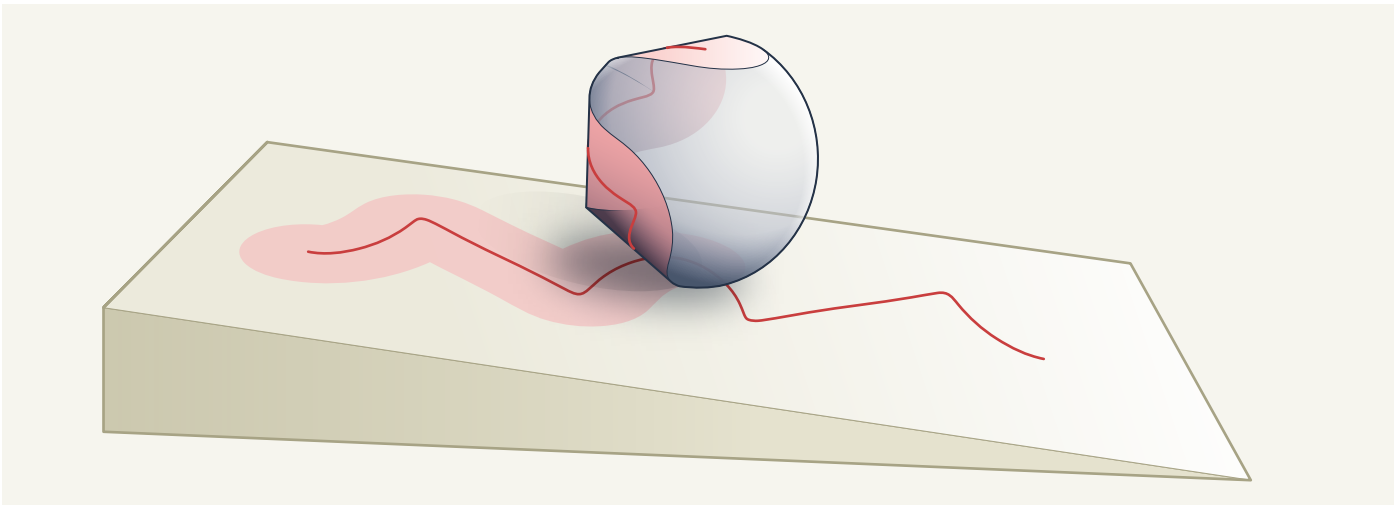

Figure 1 | How to roll on a periodic path. Sobolev *et al.*[1] devised an algorithm for constructing 3D shapes (called trajectoids) that follow periodic paths simply by rolling down a slope. The authors' approach can be understood by analogy with a clay ball rolling along a path on a tabletop. If the ball is flattened into the table as it rolls, its shape will encode the path, and it will follow this path when it rolls down a slope.