swinging-ball toy beloved by physics teachers and chief executives alike[4].

Many models for integrable systems have been proposed so far, and such models provide an excellent means of benchmarking quantum computers. However, these descriptions are usually independent of time, and quantum processors are better suited to simulations of periodic dynamics that run in discrete steps. An integrable model for periodically driven, many-body discrete quantum dynamics, known as the XXZ circuit, was proposed four years ago[5,6], and was shown to have stable quasiparticles that can form bound states[7] — a surprising result for a system in which the dynamics are driven such that the system never reaches equilibrium. The model thus provides an ideal benchmark for a quantum computer.

Morvan *et al.* performed a quantum simulation of an XXZ circuit comprising a ring of 24 qubits. These could interact with each other through superconducting currents, in which charge carriers flow without any resistance, and were able to host trapped photons (light particles). The authors first prepared the system with a string of photons, and then drove it by periodically applying a quantum logic gate to all adjacent pairs of qubits in the ring, allowing the photons to move between qubits (Fig. 1a). Single photons hopped around the ring, but so did strings of photons, and the authors clearly demonstrated that these bound states could involve up to five photons.

The experiment is extremely versatile, because the driving is implemented with a robust type of gate known as an fSim gate, which can be applied rapidly and with high fidelity. Morvan and colleagues' implementation involved the original two-parameter XXZ circuit[6] with a third parameter that they used to mimic an external magnetic field.

The XXZ circuit is the driven analogue of a well-established model for magnetism in a one-dimensional system (the XXZ model) that can be obtained from the XXZ circuit by supposing that the frequency of the driving is infinite. In the XXZ model, the excitations are bound states of magnons, which themselves are excitations of the intrinsic angular momenta of electrons in a material[8]. The corresponding relationship between the velocity and momentum of quasiparticles in the (driven) XXZ circuit has previously been predicted[7], and Morvan *et al.* corroborated this by directly observing the velocity of stable bound states associated with a one-dimensional chain of photons. This measurement complements a less-direct observation of the same relation in a solid-state system using neutron-scattering experiments[9].

Each qubit in Morvan and co-workers' experiment has a remarkably long coherence time, which is the duration for which a qubit can remain in a given quantum-mechanical state. However, the experiment is not without difficulties. The main challenge seems to be that the photons can 'leak' out of the system during the many cycles over which the qubits maintain coherence. The ideal XXZ circuit does not allow this: the total number of excitations (and thus photons) must remain constant. The authors fixed this problem by selecting only qubit sequences for which the number of excitations was conserved.

Beyond benchmarking with the XXZ model, Morvan and colleagues' work contains the conceptually intriguing, albeit speculative, suggestion that a quantum processor can probe the limits of integrability; these are inaccessible to standard classical computation when the system size is large. The bound states of photons are expected to be stable in integrable systems, and to decay quickly to equilibrium in systems that are not integrable. So the authors measured the decay of bound states for a situation in which the system should not be integrable.

They implemented this in a rather unorthodox fashion — specifically, by attaching an extra qubit to every other qubit in the ring, using an fSim gate (Fig. 1b). They found that the decay of the fraction of photons in bound states was surprisingly slow. Instead of decaying quickly, the bound states survived for up to 40 experimental cycles with a probability that was close to one, even when the ring qubits were coupled to the extra qubits as strongly as they were to each other.

In my view, this is potentially the most remarkable result of the paper, and it invites further in-depth analytical, conceptual and simulation studies of the problem. It is possible that this phenomenon shares similarities with the non-ergodic behaviour of another non-integrable periodic XXZ model, which was previously revealed in classical simulations[10]. There are also hints that it could be explained by some (quantum) form of the Kolmogorov–Arnold–Moser theorem, which quantifies the stability of classical integrable systems when they are subjected to perturbations[11]. Regardless of the underlying mechanism, Morvan and colleagues' result is a tantalizing example of what can currently be achieved with quantum processors.

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Alzheimer's disease

Swollen axons impair neuronal circuits

Inma Cobos & Jorge J. Palop

Abnormal protein aggregates are a hallmark of Alzheimer's disease. It emerges that these plaques cause swellings in neuronal projections called axons that prevent proper circuit function. **See p.328**

Alzheimer's disease is characterized by the abnormal accumulation of two misfolded proteins — amyloid-β, which forms structures called plaques outside cells, and tau inside cells. However, the effect of these aggregates on neuronal and network functions has been difficult to assess. The highly aggregated amyloid-β that makes up the core of plaques is surrounded by areas in which the synaptic connections between neurons have been lost[1,2], and by neuronal projections called axons that have abnormal swellings, known as dystrophic neurites. Are these dystrophic neurites inert, or do they drive disease progression? On page 328, Yuan *et al.*[3] outline evidence suggesting that dystrophic neurites impair neuronal-circuit function, and provide mechanistic insights into this process.

The authors used high-resolution, time-lapse imaging to study single axons with

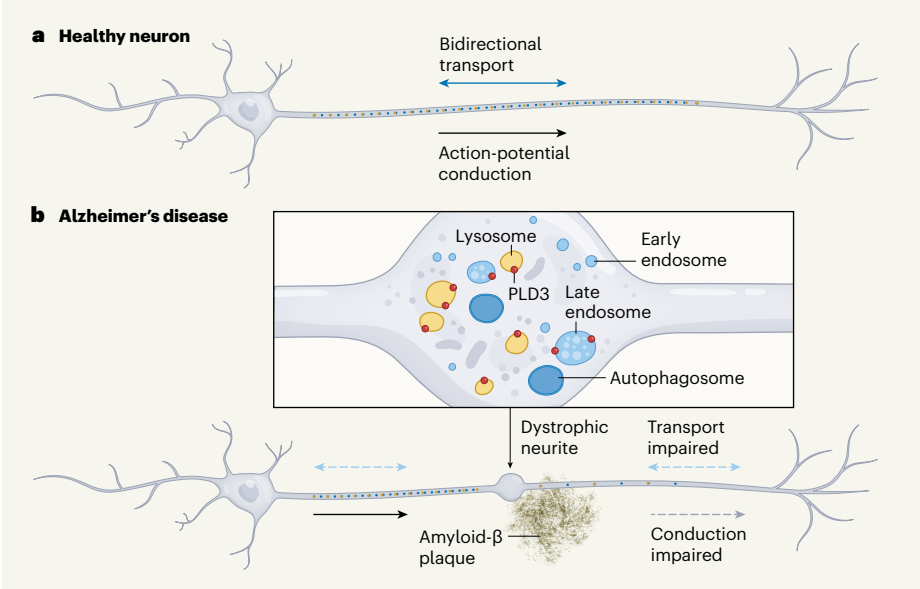

Figure 1 | Axonal swellings alter neuronal function. a, In healthy neurons, electric currents are conducted down axons in waves as action potentials. A range of molecular cargo is transported in both directions between the neuronal body and neuron terminal, including various types of vesicle and organelle. **b**, In Alzheimer's disease, plaques of the protein amyloid-β accumulate outside neurons. Plaque-associated swellings called dystrophic neurites form in axons, impairing cargo transport. Yuan *et al.*[3] find that dystrophic neurites are filled with a range of vesicles (labelled in inset box) involved in two protein-breakdown pathways, the endolysosomal and autophagic pathways. Some of these vesicles are abnormally large and express the protein PLD3. The authors show that dystrophic neurites impair the conduction of action potentials through a PLD3-dependent mechanism.

or without plaque-associated dystrophic neurites in live mice. They estimated that each plaque contained hundreds of axons that carried dystrophic neurites. The size of the swellings changed dynamically over extended periods, even months. Some returned to normal without loss of the axon, indicating that the swellings are not necessarily indicative of degenerating axons.

To test whether dystrophic neurites cause axonal dysfunction, Yuan *et al.* measured influxes of calcium ions (which accompany waves of electrical activity called action potentials in neurons) between and within the brain hemispheres. They found that the increased volume of axonal swellings (compared with the volume of normal axons) acted as a sink for waves of electrical activity, reducing conduction speeds and even blocking action-potential propagation (Fig. 1). Because the brains of people in the advanced stages of the disease contain more than 20 plaques per square millimetre (ref. 4), axonal conduction abnormalities might be an important mechanism for neural-network dysfunction in Alzheimer's disease.

Dystrophic neurites are hotspots for intracellular accumulation of Alzheimer's-related proteins, including tau and amyloid precursor protein[2,5]. They also act to block bidirectional transport of biomolecules between the neuron's cell body and its synaptic terminals[2,5]. Yuan *et al.* found that abnormally enlarged vesicles and multivesicular bodies accumulated progressively in developing dystrophic neurites. Each neurite held a variety of these organelles, perhaps reflecting the several types of vesicle involved in two protein-degradation processes — the endolysosomal pathway and autophagy.

The researchers asked whether the protein phospholipase D3 (PLD3) might mediate dystrophic-neurite formation. The protein is found in vesicles of the endolysosomal pathway and regulates their size. Several variants of the *PLD3* gene, including one dubbed V232M, have been linked to increased risk of Alzheimer's disease in some human populations[6] (although not in others[7]). Yuan and colleagues found that unusually large endolysosomal vesicles were more abundant in dystrophic neurites of people with Alzheimer's disease who carried the V232M variant than in those of non-carriers, suggesting that altered endolysosomal function promotes dystrophic neurites, which might increase the risk of Alzheimer's disease.

Next, the authors examined the role of the PLD3 protein using a mouse model of Alzheimer's disease. PLD3 overexpression resulted in larger dystrophic neurites with more endolysosomes. Action-potential propagation was hampered more in animals that overexpressed PLD3 than in controls that did not overexpress the protein. By contrast, ablation of PLD3 reduced the average size of dystrophic neurites, and ameliorated conduction abnormalities.

It is counter-intuitive that reducing endolysosomal function through PLD3 ablation

From the archive

The many wonders of statistical analysis, and a glimpse of scientists poised on the verge of discovering insulin.

50 years ago

Statistics : a Guide to the Unknown. Edited by J. M. Tanur, F. Mosteller, William Kruskal, R. F. Link, R. S. Pieters and G. R. Rising — What statisticians do and the frequently ingenious ways they go about their mysterious work is the subject of the forty-four essays that make up this book ... [O]ur essayists ... ask and then answer questions such as the following: ... Is it true that people, and most particularly famous ones, are less likely to die in the months before their birthdays than in the months that follow? (Most interesting, of course, is what this apparent fact suggests about the power of the will to live.) ... Why is no cost-of-living index ever correct? Since either it will rain or it will not, what does the weatherman mean by forecasting a "70% probability"?

From *Nature* 8 December 1972

100 years ago

Of events in biological science in the past year I may mention one that is attracting attention at this time. In the Physiological Laboratory of Toronto University has been prepared a pancreatic extract possessing striking power over the carbohydrate metabolism of the body ... Destruction of the pancreas is well known to produce in the dog a diabetes-like condition, rapidly fatal ... The inference has long been that the pancreas produces some substance enabling the body to make use of sugar—some substance that in fact should control certain forms of diabetes. At Toronto there seems to have been secured the extraction of that substance ... Gratifying success has already attended the use of this extract in the relief of ... patients; much further research is, however, yet needed for development of the methods of extraction ... The ... advance ... is ... the striking result of steady work pursued by many various workers through many earlier years ... The Toronto investigators we may be sure would say with Pasteur, "To have the fruit there must have been cultivation of the tree."

From *Nature* 9 December 1922

would reduce the size of dystrophic neurites and improve neuronal function — why would reducing a major pathway of protein degradation be beneficial in a disorder of toxic-protein accumulation? Yuan *et al.* provided tantalizing evidence that dystrophic neurites are major sites through which extracellular amyloid-β is brought into neurons for recycling or degradation. Perhaps PLD3 ablation prevents the endolysosomal pathway from being overwhelmed by a never-ending task of degrading extracellular amyloid-β at dystrophic neurites.

This mechanism complements the idea that early inefficiencies in endolysosome–autophagy pathways in Alzheimer's disease can prevent proper breakdown of amyloid-β, promoting a cascade of events that leads to plaque formation[8]. If a faulty endolysosome–autophagy system triggers this cascade, Yuan and colleagues' work suggests that precise ablation of some of the pathway's components might increase axonal health, by preventing amyloid-β from being brought into neurons in the vicinity of amyloid plaques.

Yuan *et al.* stop short of investigating the cellular mechanisms that underlie the beneficial effects of PLD3 ablation in their animal model. Furthermore, it remains unclear exactly how PLD3 variants increase the risk of Alzheimer's disease and promote accumulation of organelles in dystrophic neurites. Until this knowledge gap is filled, it is premature to propose PLD3-based interventions as potential therapies. Nevertheless, the study provides strong evidence that dystrophic neurites and PLD3 play a crucial part in nerve-conduction deficits in Alzheimer's disease.

It's been more than 30 years since synaptic abnormalities and loss were identified as the earliest, best predictors of cognitive decline in Alzheimer's disease[9]. Synaptic dysfunction (including synapse loss and defects in the plasticity of synaptic connections) is triggered by low concentrations of soluble amyloid-β, and is independent of insoluble amyloid plaques[10,11]. These and other findings cemented the idea that Alzheimer's disease is fundamentally a disorder of synaptic failure and brain-network dysfunction[12,13] — an idea strengthened by the finding that amyloid-based therapies effectively clear plaques, but produce little cognitive benefit[14]. Now, Yuan *et al.* provide support for the relevance of the plaque microenvironment, and potentially point to an inability of amyloid-based therapies to resolve axonal impairments after plaques are cleared[15]. Going forward, approaches to analyse the function of neuronal circuits and networks in the human brain will be needed to truly understand the mechanisms that underlie this disease, if we are to develop successful therapeutics to treat it.

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Microbiology

A viral cocktail calms gut inflammation

Alice Bertocchi & Fiona Powrie

Abnormalities in gut bacteria can contribute to hard-to-treat illnesses, such as inflammatory bowel diseases. Efforts to harness bacterium-targeting viruses reveal a promising way to tackle these conditions.

Inflammatory bowel diseases (IBDs) are chronic conditions of the gut in which genetic and environmental maladaptations drive a breakdown in communication between the cells of the host and the diverse gut bacteria, termed the microbiota[1,2]. Writing in *Cell*, Federici *et al.*[3] present their highly ambitious and systematic approach to targeting bacteria associated with the development of IBD.

The composition of the microbiota varies substantially from person to person, but dysbiosis — lower-than-normal richness and diversity of gut-bacterial species — is a common feature of IBD[2]. This reduction in diversity is associated with an impaired immune response and problems with the cellular barrier that usually blocks bacterial entry from the gut lumen into gut tissue. These malfunctions can cause problems with antibacterial defence mechanisms, leading to the emergence of potentially disease-causing bacteria that thrive in an inflamed gut. Such observations have fuelled attempts to target dysbiosis in IBD. However, therapeutic approaches ranging from drugs such as antibiotics to the use of faecal transfers to populate the microbiota have yielded mixed and inconsistent results[2,4].

The authors harnessed bacteriophages (also known as phages) — viruses that can infect and kill bacteria. Phages can specifically target particular bacterial strains, and therefore offer a therapeutic strategy for IBD in which one or more specific disease-causing bacteria are selected for destruction[5]. Federici and colleagues show that an orally delivered cocktail of phages that target an IBD-associated strain of the bacterium *Klebsiella pneumoniae* attenuated intestinal inflammation in mice (Fig. 1), providing a proof of concept for the use of phage therapy for this condition.

Klebsiella pneumoniae is frequently present in oral tissue, but can colonize the gut during dysbiosis, sometimes leading to inflammation[6]. Federici and colleagues collected clinical data from people with IBD and from healthy individuals in four locations around the world. The authors observed that 39% of people with IBD had an increased proportion of *K. pneumoniae* in their stool samples compared with healthy individuals. This also indicates that *K. pneumoniae* colonization of the gut occurs across many diets and lifestyles. Previous work identified a strain of *K. pneumoniae*, called Kp-2H7, in the saliva of people with IBD, that triggers a pro-inflammatory response in the mouse gut[6].

Federici *et al.* investigated *K. pneumoniae* strains in their human samples using a DNA-sequencing approach followed by bioinformatic analyses, and identified one strain (which they named Kp KSB1_4E) as being significantly more abundant in people with IBD than in healthy individuals. Interestingly, this strain belongs to the same genetic branch (clade) as Kp-2H7, which the authors term collectively as an IBD-associated Kp2 clade.

To test whether such Kp2 strains have a causal role in driving gut inflammation, the authors isolated Kp2 and non-Kp2 strains from stool samples of people with IBD, and tested the functional features of these strains using *in vivo* tests in mice. When introduced into