of the authors' device have demonstrated that quantum effects can be used to find solutions to optimization problems[8]. However, these devices were not shown to have advantages over classical algorithms for real-world optimization problems[9].

In the current paper, King et al. used their device not for optimization tasks, but for its more promising 'native' function of simulating quantum systems. In a model of a quantum magnet, the '0' and '1' states of a qubit in the device could correspond to the magnetic moment of a localized electron pointing up or down.

The authors simulated a particular quantum-magnet model in which competing interactions between magnetic moments give rise to a phase of matter that can be described by moments pointing in any direction on a plane. At zero kelvin, all of these moments are aligned (Fig. 1a). However, at non-zero temperatures, features known as topological defects emerge. Two such defects are vortices and antivortices — points around which moments rotate clockwise or anticlockwise, respectively, when circling the point in a clockwise direction (Fig. 1b).

At low temperatures, defects show up as tightly bound pairs of vortices and antivortices. As the temperature is increased, the system undergoes a phase transition in which these pairs of defects unbind to form isolated vortices and antivortices[10,11]. Work on this transition resulted in the 2016 Nobel Prize in Physics (see go.nature.com/2napzlx). The phenomenon has been observed in liquid-helium films[12], layered magnets[13] and ultra-cold atomic gases[14]. King et al. realized the transition in their quantum simulator, suggesting that such devices could be used to study this transition and others in a variety of models.

As interesting as the observed phase transition is, the main strength and impact of the paper is not in the specific model, but rather in the demonstration that reliable programmable quantum simulators that have more than 1,000 qubits can be built. Previous generations of King and colleagues' device had many defective qubits[8,9], but the current study required a perfect array of working qubits. This requirement was met thanks to improvements in the authors' fabrication technology over the past decade.

King and colleagues' observations are consistent with state-of-the-art classical simulations, showing that the results obtained by such quantum simulators can be trusted. This is an exciting development, as I have argued previously that the authors' device could have greater potential for quantum simulation than for optimization problems.

A limitation of the current device is that it can realize only what are known as stoquastic quantum models. These can be mapped to corresponding purely classical models and can, therefore, be simulated on classical computers. Although this mapping allows experiments to be compared to classical simulations, it limits the usefulness of the quantum simulator. To go beyond what is tractable on classical computers, two avenues of further development could be explored.

The first is to carry out quantum simulations of dynamical non-equilibrium effects, such as the propagation of excitations that occurs after the system of qubits is perturbed. Such effects are difficult to simulate classically, even in the case of stoquastic models. However, in contrast to quantum simulators built from dilute ultracold atomic gases or trapped ions, solid-state devices such as that made by the authors are subject to substantial environmental noise from lattice vibrations, and from electric-charge and magnetic-field fluctuations. This noise destroys the purely quantum evolution of the qubits. The design of qubits that have low sensitivity to noise will therefore be crucial for the study of quantum dynamics using solid-state quantum simulators.

The second direction for future development is to introduce other types of programmable interaction between the qubits that would realize non-stoquastic models for which no efficient classical simulators exist. Such models include those of frustrated quantum magnets, in which competing interactions give rise to unusual quantum phenomena, and to phases of matter that contain exotic types of excitation. A programmable quantum simulator for such models would open up entirely new approaches for studying complex quantum systems. ■

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MEDICAL RESEARCH

Diet boosts cancer–drug effectiveness

A drug that slows cancer growth has been found to elevate the level of the hormone insulin. This insulin rise lessens the drug's effectiveness, but a diet that lowers insulin can increase the benefits of the therapy in mice. SEE LETTER P.499

MICHAEL POLLAK

Most studies of the causes of resistance to cancer treatment focus on the tumour itself. However, some resistance mechanisms might involve alterations in the host rather than the cancer. A particularly conspicuous gap in our knowledge concerns the possibility that dietary factors influence the outcome of some cancer treatments. This has been widely assumed not to be the case, but writing in *Nature*, Hopkins et al.[1] show that cancer drugs that inhibit the signalling protein PI3K are considerably more effective in mice if the animals are on a specific diet. The authors provide a plausible mechanism for why this is so.

A person with cancer might wonder whether their diet could affect their prognosis. A wide range of dietary recommendations are available, both on the Internet and from physicians and dieticians. Such advice is often conflicting. For example, a patient might read that extreme dietary calorie restriction helps to 'starve' a tumour in a clinically useful manner, but might also come across information suggesting that the opposite approach of maximizing calorie intake is beneficial, to avoid cancer-associated weight loss linked to later stages of the disease. Clinical data to support either of these approaches are not compelling. Physicians lack high-quality data on which to base dietary advice for people undergoing cancer treatment.

Hopkins and colleagues now provide evidence from mouse experiments that a diet that keeps levels of the hormone insulin low improves the effectiveness of cancer drugs that inhibit PI3K. There is great interest in trying to inhibit PI3K signalling in cancer cells, because mutations that cause
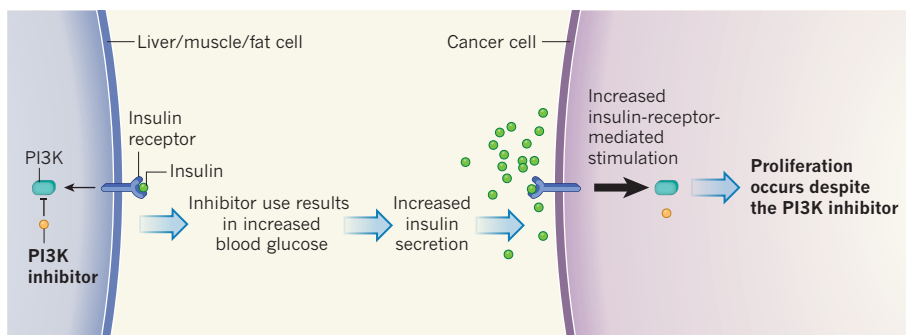
Figure 1 | Effectiveness of a cancer drug is linked to blood insulin levels. Activation of the PI3K signalling pathway can boost cancer-cell proliferation, yet the effectiveness of drugs that block PI3K to treat cancer is often disappointing. PI3K acts in the pathway regulated by the hormone insulin, which controls blood glucose levels. Insulin is released by the pancreas (not shown) in response to high blood glucose. When insulin binds to its receptor on liver, muscle or fat cells, PI3K signalling in these tissues is activated, which ultimately lowers glucose in the bloodstream. However, this process can be inhibited by drugs that target PI3K. Hopkins et al.[1] report that glucose and insulin levels increased in mice that received PI3K inhibitors compared with the levels in mice that did not receive the drug. The authors found that the inhibitor-driven rise in insulin levels can enable cancer cells that express insulin receptors to proliferate despite drug treatment. This might be because insulin-receptor signalling increases sufficiently in the cancer cells to overcome the inhibitor's ability to block PI3K action. The authors found that a diet that lowers insulin levels boosts the effectiveness of PI3K inhibitors in cancer treatment in mice.

excessive activation of this pathway are common in many kinds of cancer[2]. The pharmaceutical industry has invested heavily in developing drugs that inhibit the PI3K signalling pathway, but most clinical trials of these agents have revealed only modest benefits.

The authors offer a fresh perspective on the effect of PI3K inhibition by taking into account the fact that these inhibitors not only target cancer cells, but also act on tissues that regulate blood glucose levels. In glucose regulation, insulin is secreted by the β-cells of the pancreas when blood glucose levels rise. Insulin binding to receptors on its target cells activates the PI3K signalling pathway in liver, muscle and fat, causing changes in glucose production and uptake that reduce the glucose concentration in the bloodstream.

Cancer cells commonly also express insulin receptors, and, as in normal cells, signalling through the insulin receptor activates the PI3K signalling pathway. However, in cancer cells, pathway activation causes an increase in cell proliferation and a reduction in cell death, rather than affecting blood-glucose regulation. This is in keeping with the observation that insulin-like hormones and the PI3K signalling pathway are both ancient in evolutionary terms[3,4], and their roles in stimulating cellular nutrient use and proliferation pre-date their function of blood-glucose regulation.

Hopkins and colleagues' results confirm previous reports[5–7] that PI3K inhibitors raise blood glucose by blocking signalling downstream of the insulin receptor in tissues involved in blood-glucose regulation. The authors go on to show that this increase in blood glucose causes a substantial elevation in insulin levels in the bloodstream. This rise in insulin probably results from pancreatic β-cells responding to high blood glucose concentrations by secreting extra insulin

in an attempt to restore normal glucose levels. The authors make the key finding that, in cancer cells that express insulin receptors, this rise in insulin is sufficient to increase signalling downstream of the insulin receptor to activate PI3K and overcome the action of the PI3K inhibitor on the pathway (Fig. 1). This lessens the drug's therapeutic effect and enables cancer cells to proliferate despite drug treatment.

Furthermore, Hopkins et al. show that combining a PI3K inhibitor with a pharmaceutical or dietary intervention that lowers blood glucose reduces the drug-induced elevation in insulin, and that this increases the effectiveness of PI3K inhibitors in slowing cancer growth, compared with the effect of the drug in animals that do not receive a glucose-lowering intervention. The most effective intervention tested was a type of low-carbohydrate, high-fat diet termed a ketogenic diet, which improved the action of the PI3K inhibitor to a greater extent than was observed for the drug metformin, which reduces glucose output from the liver, or for the drug canagliflozin, which causes glucose loss in the urine. Notably, the authors found that a ketogenic diet in the absence of the inhibitor drug did not curb cancer growth in mice. Consistent with this, early-stage clinical trials have not shown that this diet alone improves cancer survival[8].

Hopkins and colleagues' findings are important because they identify a mechanism of resistance to cancer therapy that is based on a hormonal response of the host, rather than on alterations in cancer cells. The key element of this response is a rise in insulin levels, but whether other hormones involved in

> *"Differences in diet could contribute to variability in response to cancer treatments."*

regulating glucose metabolism also contribute to the effect is not known. Previous research[9] indicates that high insulin levels associated with obesity can increase the risk of cancer or worsen prognosis. The work by Hopkins et al. reveals an additional connection between insulin and cancer by illuminating a way in which this hormone can influence the usefulness of a cancer drug.

Certain PI3K-inhibitor drugs block only the δ version of the protein, which is found in blood cancers, but not in common solid tumours or in the organs that regulate blood glucose. These inhibitors presumably do not significantly elevate blood insulin levels, so the mechanism of resistance described by Hopkins et al. does not occur. If this is the case, it might help to explain why this particular type of PI3K inhibitor was the first to show sufficient activity in clinical trials to be approved for clinical use.

Hopkins et al. provide a firm basis for investigating dietary or pharmaceutical approaches to reduce insulin signalling in cancers to enhance the effectiveness of PI3K inhibitors. The authors' data indicate that previous attempts[10] to predict whether this class of drug would be effective by examining tumour characteristics would have overlooked the part played by host insulin levels.

Substantial patient-to-patient variability in the response to anticancer drugs often occurs even among patients whose tumours show similar genetic abnormalities. Along with another paper[11], published last month, which demonstrates that a diet rich in the amino acid histidine can increase the effectiveness of the anticancer drug methotrexate, Hopkins and colleagues' study supports the idea that differences in diet could contribute to variability in response to cancer treatments. Excitingly and unexpectedly, we now have a rationale for clinical research to determine whether the efficiency of certain cancer drugs might be improved by pairing them with specific diets. ∎

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