Where does this speed-up come from? As with most quantum enhancements, it is difficult to ascribe it to any one feature of the quantum system. Layden *et al.* offer numerical evidence that their chosen quantum operations strike a delicate balance between generating proposals that are diverse with ones that satisfy the constraints imposed by the target probability distribution — a trade-off that classical proposal strategies struggle to achieve.

Although Layden and colleagues' work is comprehensive, there are some limitations. First, the proof of convergence of the quantum-enhanced algorithm is valid only if the quantum operations are executed perfectly — in the absence of any noise arising from the hardware. However, their experimental results suggest that the rate of convergence is somewhat robust to noise, especially if the hardware noise can be randomized. Second, the accelerated convergence was observed only for small-scale problems, and could disappear at larger scales, especially in the presence of noise. If the authors' explanation for the reason for the speed-up is valid, and if hardware noise can be suppressed at larger scales, it seems likely that the speed-up would persist, but this is far from certain at this stage.

Finally, although Layden *et al.* have demonstrated that their quantum-enhanced algorithm shows faster convergence than do some common classical proposal strategies, there are many MCMC variants that they haven't tested. It is therefore possible that this gap could be closed by other classical proposal strategies that exist or could be devised — perhaps even some that are inspired by this work. Despite these limitations, Layden and colleagues' research forges an important and exciting application of early-stage, noisy quantum computers to generate useful solutions and, in doing so, it defines many directions for fruitful future research.

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Cell division

A lack of commitment to proliferation

Alexis R. Barr

It turns out that commitment to cell division is not an irreversible switch. In the absence of sustained stimulation by growth factor proteins during DNA replication, cells can quit the cell cycle before cell division occurs. **See p.363**

When cells proliferate, they commit to replicating their DNA and then dividing the duplicated genome and cellular contents into two new cells. This commitment to proliferation is dependent on proteins called growth factors (also known as mitogens) and has been likened to an irreversible switch, termed the restriction point, that occurs before DNA replication starts. According to that model, if growth factors are withdrawn before this molecular switch is flipped, cells will return to a non-proliferative state called quiescence (also known as G0). But if they are removed after this switch has been flipped (Fig. 1a), cells will complete a round of DNA replication and cell division before re-entering quiescence[1,2]. Or so we thought. On page 363, Cornwell *et al.*[3] present data that challenge this model.

The authors show that cells that were thought to be irreversibly committed to proliferation by the flipping of this switch do not necessarily complete cell division. Instead, Cornwell and colleagues show that if growth factors are withdrawn after the proposed switch has been flipped, the cells sometimes just replicate their DNA without dividing. Intriguingly, whether a cell completes cell division or withdraws from the cell cycle can be attributed to the amount of a single protein — cyclin A2.

This work stems from the authors' initial observation that if growth-factor signalling was disrupted after human cells had flipped the switch, a small population of the cells (up to 15%, depending on the cell type) did not complete cell division and only replicated their DNA. Therefore, about 15% of cells were not committed to cell proliferation. Using single-cell time-lapse imaging, the authors were able to

From the archive

Concerns about preventable cases of infant death, and praise for a museum guide book about fossils.

50 years ago

[A] meticulous study of birth records in New York City ... involved examining the records of all the births which took place ... in 1968 ... If all the women ... had received adequate prenatal care, infant mortality could have been cut by one third, the study suggests ... Small wonder, therefore, that Dr Robert Coles of Harvard University said in a preface to the report that "we do things wrong, we are indifferent to the needs of others — and here, right here is the proof."

From *Nature* 13 July 1973

100 years ago

British Museum (Natural History). Guide to the Exhibition Galleries of Geology and Palaeontology — The Keeper of Geology, in his preface to this small book, says, "It is merely a guide, not an introduction to the study of fossils." Those familiar with official scientific publications may appreciate the modesty and wisdom of this statement. But intelligent members of the general public ... will soon find that the statement errs on the side of diffidence; they will say, "This is not merely a guide, but a remarkably good guide" ... The casual visitor to these magnificent geological collections is often bewildered by the multitude of objects and oppressed by the strangeness of nomenclature. With this guide ... the systematic names are explained in everyday terms and the essential characters of the fossils are made clear, while no opportunity is lost of showing how the forms of these extinct creatures throw light upon their habits and phylogeny. Thus a great deal of sound information is woven into a readable story, which does not neglect human interest but links up the fossils with their discoverers or with some apt reference to literature or history. Who will not be tempted after reading of Thomas Hawkins to look up his descriptions of the hunt for Ichthyosauri, or to renew an acquaintance with "The Chambered Nautilus" of Oliver Wendell Holmes?

From *Nature* 14 July 1923

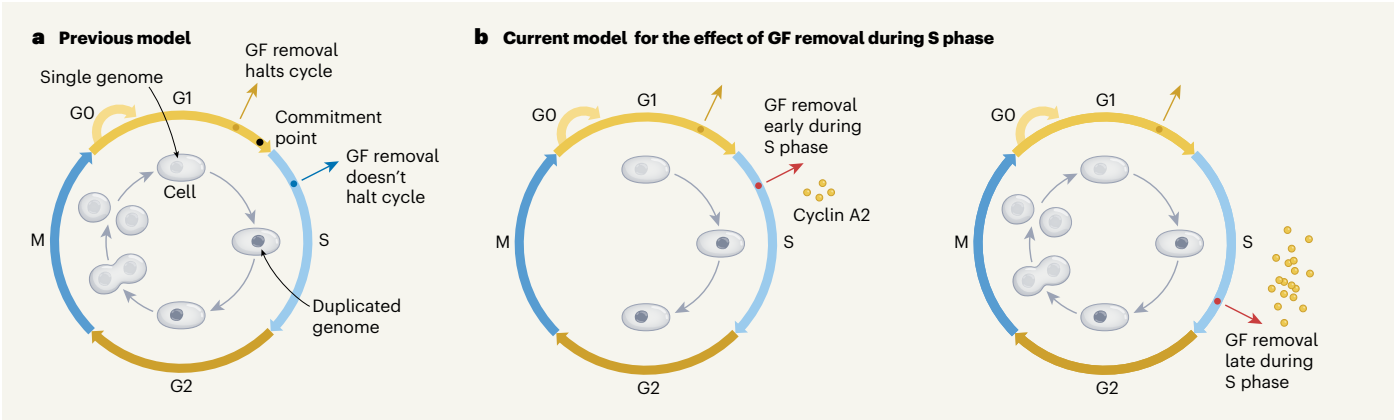

Figure 1 | Cell division without commitment. a, Cells going through cell division go through stages termed G1, S, G2 and M, during the course of which they duplicate their genome. Previous models of the cell cycle pointed to an irreversible commitment point or switch during the G1 phase, before DNA replication. If proteins called growth factors (GFs) were withdrawn in the G1 phase, and before this point, cells would not proliferate and would instead revert to a non-proliferative state termed G0 (also known as quiescence). However, if growth factors were withdrawn after this commitment point, it was thought that cells would complete a proliferative cycle. **b**, Work by Cornwell *et al.*[3] questions the existence of an irreversible commitment point during the G1 phase. Instead, the authors suggest that if growth factors are withdrawn early during DNA replication, which occurs in the S phase, this leads to a fall in the level of the protein cyclin A2 and results in cells completing DNA replication but withdrawing from the cell cycle during G2, before cell division occurs. If growth factors are withdrawn late in the S phase, however, sufficient cyclin A2 protein remains to enable cell division.

simultaneously measure molecular events and monitor cell behaviour to determine how this subpopulation of cells could arise.

Cornwell and colleagues describe two competing cellular outcomes: cell division and cell-cycle exit before division (Fig. 1b). Both outcomes are governed by growth-factor signalling.

When growth factors are abundant, cells complete a round of proliferation and cell division occurs. This is because growth factors stimulate expression of the gene encoding cyclin A2, and when cyclin A2 protein is abundant, cells replicate their DNA and then divide. However, when growth factors are depleted, or their downstream signalling events are disrupted, cell-cycle exit occurs. In this case, expression of the gene encoding cyclin A2 is inhibited, the level of cyclin A2 protein declines and, if the level falls below a threshold, cells replicate their DNA but do not enter cell division. This work shows that cells do not irreversibly commit to cell proliferation; instead, they display a more flexible behaviour in response to stimulation by growth factors.

These findings raise the question of what happens if cells that replicate their DNA but fail to divide are later restimulated with growth factors. In this scenario, it is important to remember that the cells already have a duplicated genome. Whole-genome duplication is known to be an early event in tumour formation, providing a permissive environment for further genetic perturbations, and so is potentially detrimental to an organism[4,5].

The authors show that cells that replicate their DNA but do not divide display a cellular marker of a type of terminal cell-cycle arrest called senescence. This suggests, although the evidence is not yet conclusive, that these cells might have permanently exited proliferative cycles. If that is the case, then these cells might pose no further threat to an organism, although they could contribute to ageing by reducing the number of fully functional cells in a tissue.

However, if it turns out that cells with a duplicated genome can re-enter proliferative cycles in response to further stimulation by growth factors, the question becomes how they might do this. Would the cells restart the proliferative cycle at the stage at which they withdrew and complete cell division before undergoing any further DNA replication? In the fly brain, during a stage of the cell cycle called G2, cells with a duplicated genome can exit the cell cycle and enter a state of quiescence before cell division[6]. This suggests that quiescence at the G2 stage might be a normal cellular response that can occur before division happens. Alternatively, would those human cells with a duplicated genome reset and complete another round of DNA replication before cell division, thereby exacerbating the problem of genome duplication? A similar situation has been suggested before for human cells[7].

For the treatment of breast cancer that has spread, the success of drugs that target key drivers of cell proliferation, the enzymes CDK4 and CDK6 (CDK4/6), has refocused interest in inhibiting proteins that function in mechanisms that control the cell cycle[8]. Unpicking the molecular mechanisms of cell proliferation is therefore crucial to predicting the consequences of using these types of drug in the clinic.

The role of CDK4/6 in driving cell proliferation was thought to be restricted to a stage before the flipping of the irreversible cell-cycle commitment switch. However, from Cornwell and colleagues' work, as well as the findings presented by another group earlier this year[9], it is now clear that CDK4/6 is required throughout the cycle of cell proliferation to promote the expression of cyclin A2. The earlier work[9] indicates that continued CDK4/6 activity can overcome the cell-cycle block that occurs on inhibition of another cell-cycle driver, the enzyme CDK2, by maintaining high expression of cyclin A2. The findings about CDK4/6 further corroborate observations[10] initially described in 2019.

This work by Cornwell *et al.* is yet another demonstration of how high-throughput, single-cell timelapse imaging gives us the power to unpick the molecular mechanisms driving cellular phenomena that were first described around 50 years ago[2]. These types of experiment consistently reveal the notable gaps in our understanding and demonstrate how the ability to identify subpopulations of cells can give us insight into previously unappreciated molecular mechanisms.

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