coil can be viewed as a dissipation channel, whereas an amplifier connected to the emitting coil can be viewed as a gain channel (Fig. 1b). Then, if the resonant inductors are identical, and if the increase in electromagnetic energy provided by the amplifier exceeds a certain value that depends on the load, the whole system becomes parity–time symmetric. Such a system automatically selects the operating frequency that corresponds to the maximum transfer efficiency, regardless of the distance between the coils. The result is wireless power transfer that does not require static coils, a source of radio waves or a tuning circuit.

After validating their strategy using simulations, Assawaworrarit and colleagues demonstrate it experimentally. They connect a resonant inductor to an amplifier and an identical inductor to a resistor, which acts as a load. The authors observe wireless energy transfer with 100% efficiency, irrespective of the distance between the inductors, up to about 70 cm. Even more spectacularly, they show that when the resistor is replaced by a light-emitting diode, the diode's brightness is independent of the separation distance. The authors use numerical simulations to demonstrate that their system automatically adjusts its operating frequency in a period of tens of microseconds.

Assawaworrarit and colleagues' results are impressive on several grounds. First, they are a further proof that fundamental concepts from quantum mechanics — a rather obscure scientific discipline to the non-specialist — can lead to practical applications. Second, the authors' proposal substantially simplifies the design of wireless power chargers, replacing a fine-tuned source of radio waves with an amplifier. Last, and most importantly, the work opens up the possibility of robust and dynamic wireless power transfer. This idea is extremely appealing, whether it is applied to the charging of medical implants or to the powering up of moving electric vehicles.

However, realizing such applications will require further work. For instance, although Assawaworrarit *et al.* demonstrate that the efficiency of energy transfer between the coils is 100%, this is not the case for transfer between the power supply and the load. Overcoming this limitation will require a highly optimized amplifier that could be unreasonably expensive.

Additionally, the authors show that the transfer efficiency is unaffected if the receiving coil is moved along the axis that connects the emitting and receiving coils. But in practical applications, the receiving coil will probably move perpendicular to this axis — for example, in the case of an electric vehicle, the emitting coil would be in the ground and the receiving coil would be underneath the vehicle parallel to the ground. Will this affect the parity–time symmetry of the system and its behaviour? Furthermore, if the receiving coil moves at a relatively high speed with respect to the static emitting coil, will the amount of energy transferred be enough for the technology to be useful? These questions need to be answered before this beautiful concept can have real-life applications; however, it already builds an inspiring bridge between the worlds of quantum physics and engineering. ■

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EPIDEMIOLOGY

Molecular mapping of Zika spread

Evolutionary trees constructed using both newly sequenced and previously available Zika virus genomes reveal how the recent outbreak arose in Brazil and spread across the Americas. SEE LETTERS P.401, P.406 & P.411

MICHAEL WOROBEY

The spread of Zika virus in Brazil and the rest of the Americas since 2015 has been deeply troubling. Previously thought of as mild, Zika has revealed a potent capacity to damage developing neurological tissues, with devastating consequences for the children of infected mothers[1]. Three related papers[2–4] in this issue provide much-needed insight into when, where and how the current Zika outbreak emerged and spread. This understanding was gained thanks to a mixture of high-tech molecular-biology and evolutionary techniques, and low-tech sample-collection efforts.

The focus of two of the studies, by Faria *et al.*[2] (page 406) and Metsky *et al.*[3] (page 411),

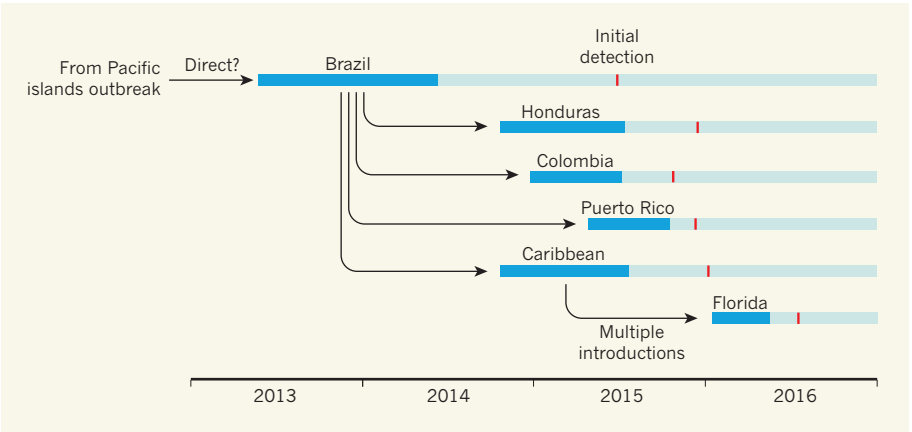

Figure 1 | Spread of Zika virus across the Americas. In three studies[2–4], collaborating groups sequenced Zika genomes taken from infected humans and mosquitoes that carried the virus, at different times and in different places across the Americas. By comparing the genetic variation between these sequences, they mapped viral spread in the region. Zika arrived in Brazil from the Pacific islands, although it is not clear whether this transmission was direct. The groups estimate that local transmission in Brazil began in late 2013 or early 2014 (possible time window indicated in blue), but the virus was not detected until mid-2015. From Brazil, Zika spread to other regions in the Americas, where initial detection again lagged months behind the estimated window for the start of local transmission. Introduction to Florida from the Caribbean seems to have occurred on several occasions. (Time frames depicted in this figure are rough estimates only; more-precise dates can be found in the papers.)

50 Years Ago

Normal tissue growth requires that cells should recognize each other and stop growing or moving at the right time and place. Understanding how this regulation is achieved is of fundamental importance. *A priori* one might expect that some kind of chemical signal passes from cell to cell. This is certainly the simplest explanation of the phenomenon of contact inhibition — cells stop moving and dividing when they come into contact with each other … Loewenstein and his collaborators … have shown that at regions of cell contact, junctional surfaces, in several tissues cellular substances diffuse rather freely from the interior of one cell to that of the next … Thus a quite large molecule could act as a signal for contact inhibition … These experiments … suggest that normal growth and differentiation of tissues depend on a flow of material from the interior of one cell to that of another.
From *Nature* 17 June 1967

100 Years Ago

M. G. Daressy has been writing concerning the long-disputed question as to the identity of one of the animals which the old Egyptians selected as the symbol of their malevolent deity, Set or Seth. Among creatures suggested as intended by the Egyptian artists have been the jackal, hare, oryx, and okapi, but all these assignments have been abandoned …
M. Daressy argues that the Set animal is really a creation of the imagination … so it is futile to search for the creature in either the existing or fossil fauna in Africa … It may be that the animal was very scarce, and that after its association with the detested deity it was exterminated by the Horus-following, orthodox Egyptians.
From *Nature* 14 June 1917

converges on South America. The groups sequenced Zika genomes from people and from *Aedes aegypti* mosquitoes, which carry the virus. Inspired by the success of real-time sequencing efforts during the Ebola virus outbreak[5], Faria and colleagues obtained several samples using a mobile sequencing laboratory deployed in Brazil. Together, these efforts produced more than 100 new genomes.

The groups used these genomes, along with some existing ones, to construct phylogenetic (evolutionary) trees of Zika in the Americas. In this way, they could reconstruct Zika's spread by following a trail of mutations — accumulated by virus strains that the authors sampled at different times and places — back to the outbreak's most recent common ancestor. These trees confirm previous evidence[6] that northeastern Brazil is the outbreak's hub.

The Zika strain that founded the American outbreak was evidently introduced from the Pacific islands[6], but the current studies cannot prove that transmission to Brazil was direct. Indeed, Faria *et al.* note that some of the deepest branches and earliest samples on the American Zika tree are from the Caribbean. Nonetheless, the collected genomes show that Zika was circulating in northeastern Brazil by late 2013 or early 2014 — more than a year before the first reported case in Brazil[7]. They also demonstrate that northeastern Brazil was the source of onward dispersal to several other countries, with an estimated 6–12-month lag between dispersal and initial detection in those regions (Fig. 1). These lag times are not unreasonable, given that it takes time for infection numbers to build up, and that the most obvious effects are seen in babies, born months after mothers have been infected.

It would be a mistake to dismiss these findings because of the 'small' sample sizes involved. Sample numbers in phylogenetic analyses are not the same as sample sizes in, for example, clinical trials. A single sequence can prove the presence of a viral strain at an early time. And, as in the current work, just a handful of strains showing substantial genetic differences can provide compelling evidence for years of undetected circulation.

Faria *et al.* and Metsky *et al.* thus provide time points from which to compare the pre- and post-Zika incidence of microcephaly — a condition in which newborns have abnormally small heads and brains — and other Zika-associated symptoms in each affected region. This comparison will allow a better understanding of the effects of the virus. The groups' work also indicates that successful jumps out of Brazil may coincide with times at which seasonal and environmental factors are optimal for viral spread by *A. aegypti*.

This last point resonates with Grubaugh and colleagues' paper[4] (page 401). These authors set out to determine how and when local transmission of Zika arose in Florida, again using phylogenetic trees from human- and mosquito-derived Zika genomes. They found evidence that Zika was introduced into Florida at least four times, several months before its presence was detected. The virus probably entered from Caribbean countries linked to Miami by substantial air and cruise-ship travel.

Miami may be unique among US cities in having the ingredients that favour Zika transmission: not only the presence of *A. aegypti*, which is found in many US cities, but also large numbers of people arriving from high-incidence Zika areas at times when the mosquitoes are prevalent. Nonetheless, Grubaugh and colleagues provide evidence that each 'successful' introduction failed to sustain a permanent infection in Miami. The transmission rate was below the crucial threshold of at least one secondary infection per primary infection, on average (a secondary infection being one contracted from another person in Miami, either through a mosquito or directly). By contrast, Faria *et al.* estimate that three secondary infections arose per primary infection in northeastern Brazil.

These papers, along with a report this year on Ebola[8], set a new standard for what can be achieved by studying disease outbreaks in tantalizingly close to real time, using rapidly obtained genome sequences analysed in a powerful computational framework[9]. Such work is possible mostly through the sustained efforts of a fairly small number of scientists supported by modest grants from a few enlightened funders. These breakthroughs not only are impressive in themselves, but also expose large gaps in current approaches to detecting and responding to potentially catastrophic disease outbreaks. Systematic pathogen surveillance is within our grasp, but is still undervalued and underfunded relative to the magnitude of the threat.

A virus-as-wildfire metaphor comes to mind in this context (possibly because I used to be a forest firefighter). In fire-prone areas of North America, lightning is expected, storms are tracked and each strike is pinpointed. Planes fly out at first light to look for smoke near each strike point, and firefighters are on site the same morning. This mentality needs to be applied to emerging infectious diseases. The responses to the recent Ebola and Zika outbreaks undoubtedly involved great courage and ingenuity, but they have looked too much like valiant bucket brigades organized after the fire is out of control. We should be detecting such outbreaks within days or weeks through routine, massive, sequence-based approaches — not months or years later, when clinical symptoms have accumulated.

To do this will require investment in more-comprehensive screening and archiving of animal and human biological samples (perhaps piggybacking on the millions of samples collected for other purposes worldwide each year, then discarded). It will involve developing better ways to recover and amplify viral genetic

material from low-quality samples[3,10,11]. And it can build on the techniques deployed in the current studies. We will not put out every new fire, but we will catch some — and improve our ability to respond to the ones that get away. Any illusions that this approach would be prohibitively expensive must be dispelled by the certainty of future outbreaks that will have billion- or trillion-dollar price tags and cause unacceptable human suffering. ■

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CELL CYCLE

Division enzyme regulates metabolism

Cell division requires the action of key regulator proteins called cyclins and CDKs. It emerges that a cyclin–CDK complex can regulate cell metabolism, and targeting this metabolic regulation causes tumour regression in mice. **SEE LETTER P.426**

ABIGAIL S. KRALL & HEATHER R. CHRISTOFK

Cellular metabolism is tightly coordinated with the needs of the existing cellular state. Dividing cells must duplicate their cellular components and synthesize large amounts of proteins, lipids and DNA. Yet how metabolic processes are regulated to efficiently generate this material needed for cell division is only beginning to be understood. On page 426, Wang *et al.*[1] now reveal a direct link between the regulation of the cell cycle and that of cell metabolism.

D-type cyclin proteins and their catalytic binding-partner enzyme, (either one of the cyclin-dependent kinases CDK4 or CDK6), are required for cell division. They exhibit peak activity[2] during the early cell-cycle stage known as the G1 phase, when the cell grows in size and synthesizes components needed for DNA replication and cell division. The protein retinoblastoma (Rb) is among the most extensively studied substrates of the cyclin D–CDK complex. Progression through G1 requires the action of E2F transcription factors; however, the activity of E2F proteins is blocked when they bind to Rb (ref. 3). Phosphorylation of Rb by the cyclin D–CDK complex releases E2F proteins from their inhibitory interaction with Rb, enabling cell-cycle progression. Inhibition of CDK4 and CDK6 commonly causes cell-cycle arrest in cancer cells, mainly because the Rb–E2F complex is stabilized[4]. Some cancer cells die when treated with inhibitors of CDK4 and CDK6 (ref. 4).

Investigating human tumour cells grown *in vitro*, Wang *et al.* found that CDK6 inhibition induces the death of cells that predominantly use the combination of cyclin D3 and CDK6. Unexpectedly, they discovered that this cell death did not require the presence of Rb. Wang and colleagues investigated how inhibition of CDK6 resulted in cell death that was independent of the role of Rb in cell-cycle regulation.

The authors searched for CDK targets that might be relevant to this process by looking for proteins that associate with the cyclin–CDK complex. This led to the identification of the enzymes phosphofructokinase 1 (PFK1) and pyruvate kinase M2 (PKM2). The authors demonstrated that these proteins are directly phosphorylated by a complex formed of the specific combination of cyclin D3 and CDK6.

PFK1 and PKM2 each exist in both dimeric and tetrameric forms, with the tetrameric forms being more active[5,6]. Tests to investigate the effect of phosphorylation of these enzymes gave results consistent with a model in which phosphorylation inhibits the activities of PFK1 and PKM2 by reducing the formation of tetramers in favour of the less-active dimers.

PFK1 and PKM2 function in glycolysis, a key metabolic pathway that breaks down glucose through a series of intermediates to generate the molecule pyruvate. A reduction in the activities of PFK1 and PKM2 results in the accumulation of glycolytic intermediates[5,6]. If this occurs, rather than progressing through glycolysis to give pyruvate, these intermediates can feed into metabolic pathways known as the pentose phosphate pathway and the serine synthesis pathway (Fig. 1). The former yields the carbohydrate ribose, and the latter the amino acids serine and glycine, which are all important substrates for nucleotide synthesis. The two pathways also generate the cofactor molecule NADPH and the antioxidant peptide glutathione, both of which can neutralize reactive oxygen species (ROS)[7].

Wang *et al.* demonstrated that phosphorylation of PFK1 and PKM2 by cyclin D3–CDK6 increased the flow of glycolytic intermediates

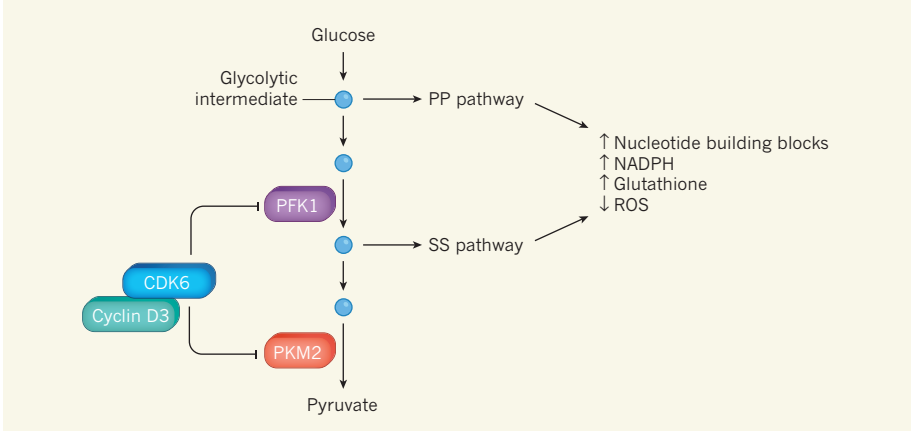

Figure 1 | Cell-cycle enzymes can affect cellular metabolism. The molecule glucose is converted to pyruvate through a key metabolic pathway called glycolysis. However, if glycolytic intermediate molecules accumulate because of a reduction in the activities[5,6] of the glycolytic enzymes PFK1 and PKM2, these intermediates can enter the pentose phosphate (PP) pathway or the serine synthesis (SS) pathway, respectively. The action of these other pathways increases levels of nucleotide building blocks, the cofactor molecule NADPH and the peptide glutathione, and decreases the amount of reactive oxygen species (ROS), which can cause DNA damage. Wang *et al.*[1] provide evidence that the cell-cycle regulatory complex of cyclin D3 protein and the kinase enzyme CDK6, which is associated with the G1 phase of the cell cycle[2], can inhibit the activity of PFK1 and PKM2, providing a direct link between the cell cycle and cellular metabolism.