

that a persistent abnormal interferon response — elevated expression of interferon-stimulated genes — is linked to increased viral load and disease severity during the chronic phase of HIV infection. Thus, both continuous administration of interferon and persistent elevation of interferon-stimulated genes are associated with unfavourable outcomes in chronic HIV and SIV infection.

HIV is not thought to become resistant to interferon in chronic infection — in fact, recent data suggest the contrary¹⁰. Instead, there is increasing concern that when the host cannot clear an infection, continued interferon signalling leads to the induction of immunosuppressive pathways with the aim of limiting damage associated with chronic infection (reviewed in ref. 11). This concept resonates with the idea of ‘tolerance’, in which the host attempts to reduce the negative impact of an infection without directly affecting pathogen burden¹². Tolerance is frequently observed in non-pathogenic SIV infections in natural hosts — animals may have a high viral load but there is minimal pathogenesis, and the interferon response normalizes after the initial stage of infection⁹. Unfortunately, in HIV infections the host rarely finds the sweet spot between viral load, disease and interferon: tolerance is rarely observed in humans¹³ and progressive immunosuppression almost always ensues.

Overall, there are strong parallels between the effects of deliberate interferon administration in experimental SIV infections and the outcome of endogenous interferon responses in natural HIV and SIV infection (Fig. 1). Sandler and colleagues’ research highlights the importance of the timing and duration of interferon administration, but also underscores the difficulty of understanding the exact potential of intervening in the interferon signalling pathways during infection.

The interferon response, and more broadly, the innate immune response, remains a field of unknowns¹⁴. Challenges include identifying the exact set of effector molecules, their roles at portals of entry of pathogens and their individual actions in acute and chronic disease. Thus, deconvoluting the interferon response is needed if the aim is to better use this pathway for therapeutic purposes. The complex antiviral response to this protein can be summarized by the Cantonese expression ‘equipped with knives all over, yet none is sharp’ — a fitting metaphor for the failure of interferon to cut cleanly through HIV infections. ■

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QUANTUM PHYSICS

The path most travelled

Continuous tracking of the random trajectories of a superconducting quantum system as it evolves between two selected initial and final states has allowed researchers to determine the most probable path of the system. [SEE LETTER P.570](#)

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Trajectories of various kinds, such as those of aeroplanes and migrating birds, are a familiar part of our everyday experience. A trajectory is given, classically, by the position coordinates of an object as a function of time. In the realm of quantum mechanics, the state of an object is given not in terms of position, but rather by a more abstract mathematical construct — a vector in the Hilbert space. Nevertheless, quantum states can be

parameterized by a set of coordinates whose evolution in time defines quantum trajectories. For a quantum system in isolation, quantum trajectories are deterministic, bearing a deceptive similarity to classical trajectories. However, the act of observation makes quantum trajectories random, revealing their fragile character. On page 570 of this issue, Weber *et al.*¹ analyse these random trajectories and find that the most likely ones still provide insightful information about a quantum system.

To study quantum trajectories, Weber and

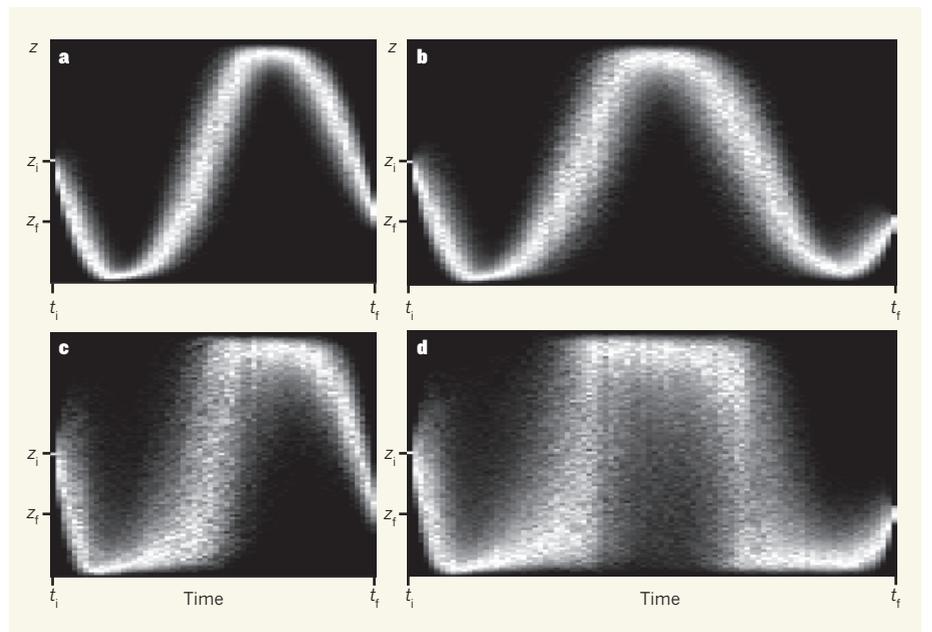


Figure 1 | Transmon trajectories. Weber *et al.*¹ have measured the evolution of the quantum state of a transmon superconducting device. The quantum state is represented by the coordinate z , and its change over time defines a quantum trajectory. In the four sets of trajectories shown here (a–d), trajectories were selected that had initial and final coordinates, at times t_i and t_f , around z_i and z_f respectively. The four panels correspond to four experiments that differ in the strength of the measurement (c and d correspond to stronger measurements) and in the total evolution time (b and d correspond to a longer evolution time). The trajectories are ‘blurred’, reflecting the randomness of the measurements and the corresponding random change of state. However, the average trajectory in each case carries information on the dynamics of the system.

colleagues used a transmon, a micrometre-sized superconducting device that at low temperatures behaves as a quantum two-state system, with states dubbed 0 and 1. The transmon and other superconducting quantum devices are under intense investigation because of their potential applications in quantum computing² and as test systems for investigating fundamental aspects of quantum mechanics³.

The authors' experiment builds on major advances in this field over the past few years. The first of these is the reduction in the 'decoherence' of transmons. Any quantum system that interacts with its environment will 'forget' its state — that is, the system will decohere. In general, this effect hampers the observation of quantum behaviour⁴ and would mask the quantum effects observed by Weber and colleagues. The second advance is the development of 'almost-perfect' measurement methods for transmons. In quantum mechanics, even perfect measurements are fundamentally limited: any single measurement provides only partial information on the state of an observed system. Moreover, after a measurement has been taken, the state of the system is changed irreversibly. The key feature of perfect quantum measurements is that the change of state following a measurement is the smallest possible allowed by the fundamental laws of quantum mechanics⁵.

Weber *et al.* measured the state of the transmon by coupling it to a device known as a superconducting resonator. The natural frequency of oscillation of microwaves in this resonator depends on the transmon's state. The authors sent microwaves to the resonator and continuously monitored how they were scattered. The scattered microwaves were processed further to extract a continuous signal containing information related to the state of the transmon.

This detection scheme involves a continuous 'weak' measurement of the transmon. Weak measurements have been investigated both theoretically⁶ and experimentally⁷. To understand this type of measurement, assume that, before a measurement is started, the quantum state of the system under investigation is well known. Next, the measurement apparatus is turned on. The measurement signal taken over a short time interval is a nearly random quantity, by itself insufficient to infer the system's state. However, the prior knowledge of the state combined with the tiny bit of information obtained from the measured signal is enough to fully infer the system's new quantum state. This process can be extended over the full duration of the measurement procedure; by using the continuous signal from the measurement apparatus, knowledge of the quantum state can be continuously updated. The change of the state over time is a quantum trajectory.

The random nature of quantum trajectories reflects the fact that the change of the quantum state at each time in the measurement process depends on the measurement result, which is

itself random. In their experiment, Weber *et al.* analyse trajectories in the following way. A set of trajectories is selected that is conditional on the initial and final states of the transmon. Although such a set of trajectories is random, the most likely one is found to provide valuable information about the transmon (Fig. 1). The most probable path is one that reflects, on the one hand, the tendency of the transmon to settle in state 0 or 1 and, on the other hand, its tendency to oscillate between these two states.

The most likely trajectory can be theoretically calculated⁸ by requiring that a global measure of the trajectory, the action, is an extremum — that is, insensitive with respect to small changes in the trajectory. This approach establishes an intriguing connection with other theories in which path optimization is key, such as Fermat's least-time principle for light propagation, the Hamilton principle for dynamics in classical mechanics, and also the formulation of quantum mechanics in terms of mathematical entities known as path integrals.

Weber *et al.* have successfully measured the statistics of quantum trajectories for their transmon device and shown that the most probable trajectory is in agreement with calculations based on extremal action⁸. An interesting parallel may be drawn with classical trajectories. Fluorescent markers can be used to characterize flow patterns or biological processes. Analogously, quantum trajectories carry information about the time dynamics of quantum systems. The use of weak measurements to determine quantum trajectories can therefore provide information about the parameters of the system that generate the dynamics. Another potential application of weak measurements is the preparation of quantum states.

Further development of the experiments described here will have to address the fidelity of the measurement procedure, which has an efficiency of 40% in its current form. The use of this method for quantum parameter and state estimation will require rigorous investigation, particularly with regard to how the method compares with similar protocols based on strong quantum measurements. ■

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50 Years Ago

At the meeting of the Society for Visiting Scientists on June 3, great interest was expressed in the potentialities of international research centres. It was admitted from the outset that there is no intrinsic merit in international research as such, since the important thing in any scientific work is the result, not how or where the work is carried out. The justification for any proposed international effort must therefore be carefully examined ... The experience of running CERN presented some interesting lessons ... CERN had been formed at a time when there was a sense of togetherness among most of the nations of Western Europe, a feeling which sought for some practical expression. It was important that any concrete form which could be given to it should not be controversial, should not be military, should not be a political disaster if it failed and that success if achieved should be clearly recognizable. If these factors were present, the way was open for the scientists, who, after all, led the world in international co-operation, to exert pressure on their political colleagues.
From Nature 1 August 1964

100 Years Ago

Many instances are on record of so-called "wolf-children," said to have been found in the jungles of India. A strange story is now reported from Naini Tal, the summer capital of the United Provinces of Agra and Oudh, of a female child about nine years old found in this neighbourhood, and unable to eat anything except grass and chapatis or native griddle cakes. She has a great mat of head hair and a thick growth on the sides of her face and spine. She bears marks of vaccination and is clearly a child who had, years ago, been abandoned or strayed into the jungle.
From Nature 30 July 1914