a rhesus monkey[4], was generated in 2001. This animal carried a marker gene encoding green fluorescent protein (GFP). Yang *et al.*[2] faced a bigger challenge in trying to introduce a disease gene into rhesus macaques.

The authors inserted a virus vector carrying part of the mutated human *HTT* gene, with 84 CAG repeats, into unfertilized monkey egg cells. The virus, which became integrated into the egg's genome, also contained a gene for GFP, the fluorescent properties of which served as a marker for the success of the transgenic procedure. Of the six resulting pregnancies, five were born at full term. Of these, three newborns carried between two and four copies of mutated *HTT*. They all developed severe symptoms of Huntington's disease and died within the first month. Of the two surviving monkeys, each of which carries a single copy of the mutated gene, one has only 29 CAG repeats and so shows no disease symptoms, and the other has 83 CAG repeats and has developed mild symptoms, which began within 1 week of birth. The authors suggest that the discrepancy in the number of CAG repeats is due to their instability during integration into the viral vector. These two macaques are still under detailed investigation for disease progression as they get older.

Previous studies[5,6] of patients with Huntington's disease have shown that the expanded stretch of glutamine residues forms aggregates in the nucleus and cytoplasm of affected neurons. Yang *et al.* found that only monkeys expressing mutated *HTT* show the anatomical changes (aggregates in neurons in both the striatum and cortex) and movement abnormalities characteristic of the disease. But the authors' transgenic monkeys show only modest signs of neurodegeneration at the tissue level, suggesting that the neuronal degeneration they observed is at a very early stage.

Researchers working on other experimental models of Huntington's disease are divided over both the exact effect of the *HTT* mutation and the temporal relationship between protein aggregation and neuronal death. Current hypotheses predict that abnormalities may occur in neurotransmission, the regulation of gene transcription, the function of mitochondria (the cell's powerhouses), and transport within axons (neuronal extensions)[7,8]. So far, the features of Yang and colleagues' transgenic primates do not favour any one hypothesis. But because of the fundamental physiological and genetic similarities between monkeys and humans (including lifespan, cellular metabolism, and endocrine and reproductive function), a primate model is more likely than other animal models to provide insights into the mechanisms of cell death associated with Huntington's disease.

In contrast to rodents, non-human primates show neuroanatomical and behavioural characteristics, both motor and cognitive, that closely resemble those of humans. For instance, primate models of Parkinson's and Huntington's diseases[9] that were generated chemically have improved our understanding of the behavioural characteristics of these diseases. But the role of genetic factors in the development of neurodegenerative diseases cannot be determined in such models. Thus, transgenic approaches (for example, local transfer of mutated *HTT* into the monkey striatum[10] or gene introduction into oocytes, as Yang *et al.* have done) seem to be the way forward in addressing the remaining crucial questions.

The primate model generated by Yang *et al.*[2] takes us another step on the long road towards developing a treatment for Huntington's disease. The history of translational (bench-to-bedside) research in neuroscience has shown a strong correlation between the availability of relevant primate models for a given disease and the development of new treatments[11]. But we must retain a healthy caution, as there is a need to determine how closely the characteristics of these authors' transgenic monkeys[2] match the spectrum of symptoms of Huntington's disease.

Yang and colleagues' approach to generating transgenic monkeys should also facilitate the development of a more elaborate model for the common form of Huntington's disease, which is characterized by a delayed clinical onset of motor and cognitive dysfunction. What's more, it opens the way to generating non-human primate models for other neurodegenerative diseases that are caused by single-gene mutations, such as familial forms of Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis. ■

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NUCLEAR PHYSICS

A neutrino's wobble?

Philip M. Walker

Periodic oscillations have been observed in what should be straightforward exponential decay curves of two radioactive isotopes. An entirely mysterious phenomenon, its proposed cause seems equally exotic.

It is a well-established fact that the rate at which a collection of radioactive atoms decays itself decays exponentially over time. It's easy to see why: the number of decays is directly proportional to the number of radioactive atoms remaining in the sample; so the fewer active atoms there are left, the fewer decays will occur. That makes observations from Litvinov *et al.*[1], in a paper in *Physics Letters B*, all the more surprising. Investigating β-decays of highly positive ions of heavy elements, these authors see a decay rate whose decline is not purely exponential, but which seems to be modulated up and down over time. They propose that the modulation arises from the 'mixing' of different types of neutrino — chargeless and almost massless particles produced in β-decays. That explanation would itself raise a host of further questions.

The observations were made at the Experimental Storage Ring (ESR) of the GSI nuclear physics laboratory in Darmstadt, Germany. The 108-metre-circumference ESR has been the scene of many experiments with highly charged radioactive ions since the early 1990s. Most of these have been precise measurements of ion masses made possible by fastidious determinations of the time ions take to circumnavigate the ring — half a microsecond, give or take. Individual ion decays have also been monitored, and their half-lives deduced. This has yielded a crop of new decay processes: an example is bound-state β-decay[2], in which the β-particle (electron) produced by the ion in its decay is captured in one of its many vacant electron orbitals.

Litvinov *et al.*[1] studied the decay of two heavy radioactive nuclides: praesodymium-140 (^{140}Pr) and promethium-142 (^{142}Pm), both from the lanthanide series of the periodic table. The nuclides, with half-lives of 3 minutes 23 seconds and 40.5 seconds respectively, were produced by smashing stable samarium (^{152}Sm) atoms into a beryllium target at more than two-thirds the speed of light. The violence of this impact strips the samarium atoms not only of almost all of their electrons, but also of several protons and neutrons — knocking off a proton and nine neutrons makes ^{142}Pm, and the loss of three protons and nine neutrons creates ^{140}Pr. With the help of magnets, the isotopes can be selected from others produced. Injected into the ESR, the precise revolution frequency for each individual ion can be obtained, so that the

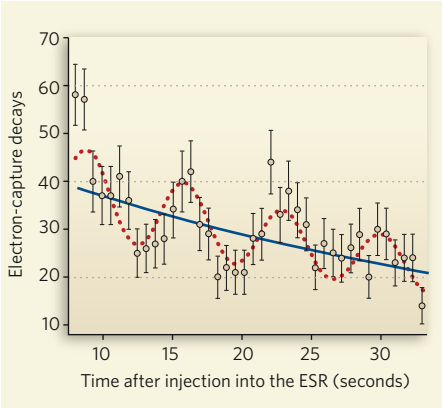

Figure 1 | Oscillating decay. Litvinov and colleagues[1] observe decay-rate oscillations with a period of about 7 seconds, here for decays of promethium-142 through electron capture, but similarly for praesodymium-140 — a phenomenon they attribute to the effect of neutrino oscillations. There are no observations for the first few seconds after formation while the ions are cooled to reduce their velocity spread.

ion's identity (mass) and decay (mass change) can be monitored.

The authors measured the process of electron capture on $^{140}Pr^{58+}$ and $^{142}Pm^{60+}$ — 'hydrogen-like' ions in which all but one of the electrons orbiting the nucleus have been removed. Electron capture is a kind of reverse β-decay in which a nucleus captures an electron from an atomic orbital, resulting in the conversion of a proton to a neutron in the nucleus and the emission of an electron neutrino. The decay products of ^{140}Pr and ^{142}Pm are thus the (stable) isotopes cerium-140 and neodymium-142; decays are signalled through a change in the ion's revolution frequency caused by a small drop in its mass. By observing many such individual decays, the decay rate is obtained, which should, as ever, fall over time as a simple exponential. What Litvinov *et al.*[1] discovered was an unexpected modulating oscillation with a period of about 7 seconds for both ions (Fig. 1).

This behaviour is perhaps all the more curious for popping up in an unusually 'clean' experimental environment. Because the radioactive ions being studied had only a single atomic electron, which went on to be captured during the decay, there are few confounding effects such as Coulomb interactions to take into account. By being confined to the high-vacuum storage ring, the ions were also effectively isolated from outside influences. In addition, only a very small number of ions — three or fewer — were allowed in the storage ring at any one time, limiting their interactions with each other.

So how are we to interpret these results? Litvinov *et al.* go to considerable lengths to rule out spurious causes such as a regular instability in the storage ring or the detection apparatus. They discuss several possible physical origins, such as the quantum-mechanical oscillation between two spin states, one of which is 'sterile', in that it is forbidden by angular-momentum conservation from decaying through electron capture. This possibility seems discounted by the fact that the overall decay rate agrees with the predictions that do not countenance a sterile state.

The authors thus argue by a process of elimination, and in agreement with a recent theoretical suggestion[3], that the modulations are due to the oscillation of neutrinos between two different mass states: that of an electron neutrino, emitted in the original decay; and that of a muon neutrino, which is observed in decays of the electron's 200-fold-heavier sibling, the muon. The generalized phenomenon of neutrino oscillation is now well documented in several contexts in which neutrinos arise — in radiation given off from the Sun, in cosmic rays, and in neutrinos produced in nuclear reactors for energy generation. In the case of heavy-ion experiments, a crucial feature is the minimal recoil energy of the ion as it decays emitting the neutrino, which should make the period of the interference oscillation dependent on the ion's mass — potentially an unequivocal experimental signature.

A back-of-the-envelope calculation shows that Litvinov and colleagues' conjecture[1] that what they see is the expression of neutrino oscillation could be well-founded — for values of the difference in neutrino masses in the middle of the presumed range, an oscillation period of the order of 10 seconds would be expected. If the conclusion did prove to be right, it could represent a sea change in neutrino physics. Neutrinos probably make up a substantial fraction of the mass of the Universe, so it is well worth our while getting to know them better. Yet they are notoriously aloof, generally passing straight through Earth without interacting. Vast underground detectors have to be built to stand a chance of detaining a few of them. One thing the ESR findings would produce would be a way of testing the properties of neutrinos purely through the decay characteristics of heavy ions that are much more amenable to investigation — without the bother of detecting neutrinos at all.

Caution is due, as it is far from simple to get to grips with the underlying cause of the decay-rate oscillations. Experimentally, the next step must be to study another example of electron capture involving a nuclide of substantially different mass that generates a different oscillation period. The authors are planning just such a test — it will be intriguing to see whether this putative new neutrino oscillation proves to be a robust phenomenon, or as elusive as the neutrinos themselves. ■

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50 YEARS AGO

Prior to a recent television series on evolution, the producer asked the audience research department of the B. B. C. to equip him with information about the knowledgeability of potential viewers [and] their attitude towards evolution ... Viewers were asked whom they associated with evolution. One in three could give no name; the name given by far the most (by one-third of the total) was that of Darwin. A few mentioned Huxley — but as many named Einstein. Other suggestions ranged from Aristotle to Attenborough, or Marconi to Mortimer Wheeler ... About two-thirds of the sample of viewers said they themselves believed in evolution; just over a tenth disbelieved the theory, the remainder having no firm opinions. Of those who said they believed in evolution, almost half were unable to advance a reason for doing so ... Asked what would ultimately happen to man ...in descending order of frequency the forecasts were: (1) that man would suffer destruction at his own hands; (2) that he would increase his power and conquer space; (3) that there would be development of brain power, or that man would lose certain parts, such as his toes. A few thought man to be "at his peak" and not likely to change further.
From *Nature* 14 June 1958.

100 YEARS AGO

Thomas Alva Edison: Sixty Years of an Inventor's Life. By Francis Arthur Jones.— This biography should do much to disillusion the impressions which are so commonly formed about successful men, that they only have to invent something to make a fortune. It shows clearly that the only road to success is through failure. His career as a telegraph operator was most precarious, and one of his first inventions—a vote-recording machine for election purposes—was refused, really because it was too ingenious and perfect; in fact, it could not be tampered with.
From *Nature* 11 June 1908.

50 & 100 YEARS AGO