



Figure 1 The γ -secretase protein quartet, and its roles in brain development and Alzheimer's disease. Presenilin-1, nicastrin, APH-1 and PEN-2 form a functional γ -secretase complex, located in the plasma membrane and endoplasmic reticulum (ER) of neurons. The complex cleaves Notch (left) to generate a fragment (NICD) that moves to the nucleus and regulates the expression of genes involved in brain development and adult neuronal plasticity. The complex also helps in generating the amyloid β -peptide ($A\beta$; centre). This involves an initial cleavage of the amyloid precursor protein (APP) by an enzyme called BACE (or β -secretase). The γ -secretase then liberates $A\beta$, as well as an APP cytoplasmic fragment, which may move to the nucleus and regulate gene expression. Mutations in presenilin-1 that cause early-onset Alzheimer's disease enhance γ -secretase activity and $A\beta$ production, and also perturb the ER calcium balance. Consequent neuronal degeneration may result from membrane-associated oxidative stress, induced by aggregating forms of $A\beta$ (which create $A\beta$ plaques), and by the perturbed calcium balance.

functions of APH-1 and PEN-2 are the same in Notch cleavage as in APP cleavage. This is important not only for our understanding of Notch signalling, but also from a clinical perspective: existing therapeutic γ -secretase inhibitors decrease $A\beta$ production, yet probably have serious side effects because they also inhibit Notch cleavage⁶ (which is important in adults as well as embryos). In addition, although various environmental signals — such as growth-factor, neurotransmitter and cytokine molecules — affect the expression and processing of APP and Notch^{9,10}, we do not yet know if and how such signals affect γ -secretase activity. Another question is whether the expression of the four proteins varies during development, although this seems likely, given the obvious importance of γ -secretase during brain development. And are any of the proteins regulated at a level beyond the expression of their genes, for example by the covalent attachment of phosphate groups?

More specific questions concern how the members of the γ -secretase quartet interact, both physically and functionally, with one another and with their substrates. Physically, they seem to bind to one another; quite how is unknown, but they probably contain protein–protein interaction domains similar to those of other membrane proteins, such as subunits of ion channels. Functionally,

presenilin-1 is believed to be the enzyme that actually cleaves APP and Notch². If so, then nicastrin, APH-1 and PEN-2 might regulate γ -secretase activity by modifying either presenilin-1's enzymatic activity or its association with substrates. Finally, the γ -secretase complex presumably functions in the plasma membrane, where Notch and

Quantum computing

Logic gateway

Andrew Steane

Two groups have created logic gates using pairs of trapped ions. As components of a quantum computer, these gates have the potential to form part of a scaled-up, workable system.

Quantum computing often features in these pages, owing to the lively pace of research in this area. The main aim is to build a large working quantum computer, but the path towards that goal promises to reveal some wonderful physics; subtle and surprising effects are confidently expected, such as quantum error correction. Also, the rich nature and behaviour of quantum entanglement — the special correlation that causes composite quantum systems to defy description in terms of their constituent parts

APP reside. But considerable evidence suggests that presenilin-1 occurs primarily in the endoplasmic reticulum, a network of internal membranes, so this presents another puzzle.

Returning to Alzheimer's disease, one burning question is how presenilin-1, nicastrin, APH-1 and PEN-2 contribute to the aberrant APP processing and neuronal degeneration seen in this disorder. Besides increasing $A\beta$ production, presenilin-1 mutations lead to a large increase in the number of calcium ions in the endoplasmic reticulum; this may contribute to defects in neuronal communication and neuronal death¹¹. It will be interesting to see if and how these two consequences of presenilin-1 mutations are linked. It is not impossible that the alterations in γ -secretase activity and APP processing caused by presenilin mutations and other genetic and environmental factors are secondary to a primary disturbance in calcium regulation or oxidative stress. It will be important to find out whether nicastrin, APH-1 or PEN-2 modifies the effects of presenilin-1 mutations on neuronal calcium balance, and on the vulnerability of neurons.

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— is not fully understood, even for systems of only a few particles, and experimentation is essential to understand larger systems. The techniques and language of quantum computing are very powerful. They will almost certainly give birth to a new generation of ultra-precise experimental methods based on the interference properties of entangled systems, whether or not efficient quantum computers are eventually realized.

Two papers in this issue^{1,2} (on pages 408 and 412) report notable progress in what is

the essence of quantum computing, namely the controlled manipulation of entanglement. Both experiments involve quantum control of charged atoms confined in a trap in a vacuum and manipulated by laser pulses. They realize, by different methods, the basic computing operation — a controlled logic gate between a pair of quantum bits (qubits). It should be noted, however, that the other main ingredients for quantum computing — precise state-preparation and readout, and high-quality quantum memory — are already reliable and taken for granted in such ion-trap technology. The theme here is not the mere demonstration of entanglement, but something more important which I will bring out after discussing the experiments themselves.

Leibfried and co-workers² have invented and demonstrated a new technique to achieve a robust, two-qubit logic gate using trapped ions. A pair of beryllium ions sits in a single trap, and the hyperfine structure of their electronic energy states enables them to store extremely stable qubits. These internal qubit states can be represented by $|\uparrow\rangle$ and $|\downarrow\rangle$. The method is to apply an oscillating force to the trapped ion pair, but one that acts only when the ions are in different internal states: when the joint state is either $|\uparrow\downarrow\rangle$ or $|\downarrow\uparrow\rangle$, the forces on the ions are not balanced and they oscillate slightly towards and away from each other. This changes the average repulsive Coulomb force between the charged ions, and hence, while the force is acting, the energy of the states $|\uparrow\downarrow\rangle$ or $|\downarrow\uparrow\rangle$ is different from half the energy of the state $|\uparrow\uparrow\rangle$. This is the so-called phase gate, which is logically equivalent to the 'controlled NOT' operation of conventional electronics.

The oscillating force is generated by a pair of counter-propagating beams, directed at the ions. A frequency difference of 6.126 MHz between the lasers sets up a highly accurate oscillation frequency for the force. This frequency difference is deliberately chosen to be close to the natural 6.1-MHz vibration frequency of the ions in the trap, taking up an idea that Milburn *et al.*³ first proposed. Under these conditions, the quantum state of the ion pair is translated around a loop in position-momentum space, as the relative phase between the ion and laser oscillations changes. After 39 μ s, the ion and laser oscillations come back into phase with each other, closing the loop traced in position-momentum space. When the ions are prepared in a superposition of $|\uparrow\rangle$ and $|\downarrow\rangle$ states (which can be done using standard laser pulses in which the ions evolve independently), the net effect is to entangle them, because the final quantum phase of each depends on the other.

The quantum logic operation is determined purely by the area of the loop traced in position-momentum space, and not by

its shape. As a result, the gate is robust — the motion of the ions does not have to be controlled in detail (they can have thermal motion, for example) and the size of the force (determined by the laser intensity) need not be stable throughout. Leibfried *et al.*² report the controlled creation of a maximally entangled state with a success rate of 97%; most of the 3% error is due to a spontaneous energy-emission process, which is known to be avoidable in other ion species.

Schmidt-Kaler *et al.*¹ have realized a logic gate between two trapped ions with the added ingredient that the ions can be addressed individually by focused laser beams. Their logic-gate method is based on the ideas of Cirac and Zoller⁴, in which vibrational motion of the ion pair is excited selectively by imparting momentum to the ions when they absorb, or are stimulated to emit, single photons. In earlier experiments, the small separations of the trapped ions meant that they could not be controlled and read out individually. In this experiment¹, two calcium ions, separated by 5.3 μ m, are addressed by a laser beam of width 2.5 μ m. Reliable discrimination of all four double-qubit states ($|\uparrow\uparrow\rangle$, $|\downarrow\downarrow\rangle$, $|\uparrow\downarrow\rangle$ and $|\downarrow\uparrow\rangle$) in the readout is possible. This team has overcome a number of experimental difficulties using various techniques, among them an adaptation of the composite-pulse methods developed for nuclear magnetic resonance technology: where any laser pulse creates an

unwanted evolution of part of the joint state, the team identifies sequences of pulses that undo that evolution but still produce the desired (non-zero) net effect.

Until now, entangled trapped ions had been created in only one laboratory — that of David Wineland at the National Institute of Standards and Technology in Colorado, USA (the group are the authors of Leibfried *et al.*²). It is a sign of growing experimental maturity that the essential experiments are now being done successfully in more than one laboratory. Furthermore, there is an important theme running through both of these papers^{1,2}: we are seeing here efforts not merely to attain some sort of entanglement manipulation in ion traps, but to do it well.

This is essential if quantum computing is to be achieved. A quantum computer will rely absolutely on qubits and logic gates that have excellent precision and can be taken for granted. The experiments by Leibfried *et al.*² and Schmidt-Kaler *et al.*¹ represent, for me, the first hint that there is a serious possibility of making logic gates, precise to one part in a thousand or even ten thousand, in a system that could be scaled up to many qubits. ■

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Palaeontology

Combing the primate record

Robert D. Martin

Fossils of bushbabies and lorises reported from deposits of the Fayum Depression in Egypt extend the known record for this group of primates from 20 million years to approximately 40 million years ago.

Primate evolution attracts special interest because of its direct relevance to human origins. The fossil record remains extremely sparse, however, and that is particularly true of a group called the strepsirrhines, which comprises the bushbabies and lorises — together, the lorisiforms — and the lemurs. Part of that picture now changes radically with the report, by Seiffert, Simons and Attia on page 421 of this issue¹, of plausible early members of the bushbaby and loris lineages. The strepsirrhines are the 'sister group' of the haplorhines — the tarsiers and higher primates, which include ourselves. The relationships among the main groups of living primates are shown in Fig. 1.

The lemurs are found only in Madagascar, and consist of 15 modern genera and 54 species². Their palaeontological record is virtually zero. The record of lorisiforms, a

smaller assemblage of 8 modern genera and 32 species², was scarcely better: until now, the earliest known fossil representatives were three early Miocene genera from Kenya (*Komba*, *Mioeuoticus* and *Progalago*), up to 20 million years old³. Seiffert and colleagues' discovery of isolated teeth and jaw fragments of two new genera, *Karanisia* and *Saharagalago*, from late middle Eocene deposits of Egypt, improves matters considerably. Both forms share unique dental features with modern lorisiforms, notably a prominent fourth cusp (hypocone) on each upper molar, contributing to a distinctive concave posterior tooth margin. In one fell swoop, *Karanisia* and *Saharagalago*, dated at between 37 and 41 million years old, have doubled the age of the known fossil record for lorisiform primates and illuminate the African diversification of lorisiforms.

An overall assessment of morphological,