be called a fudge factor, in this case of 10 or 15 million years — close to 20%.

The precise date of major genome duplications (measured by a molecular clock) can thus be compared with major events in evolutionary history (generally measured by a different molecular clock), using one or more calibration points (fossils). The error of the estimate is high, so correlations are difficult, if not impossible, to demonstrate rigorously.

Langkjaer *et al.*[1] and Bowers *et al.*[2] circumvent this problem by using relative time. Bowers *et al.* compare pairs of genes in *Arabidopsis* with those in cabbage (*Brassica*; from the same family), cotton (from a different family), pine (a seed plant, but not a flowering plant) and moss (a very distant relative), and for each gene they compute an evolutionary tree — the gene's pedigree. From the pattern of the evolutionary tree, they can determine when a duplication occurred relative to the evolutionary origin of other species (Fig. 1). The evolutionary tree (see Fig. 2b on page 436) shows a clear duplication event, affecting many genes in the genome, that occurred before the *Brassica*/*Arabidopsis* split, and before the members of the family Brassicaceae started to diverge. Similarly, Langkjaer *et al.* show that the yeast genome was duplicated before the divergence of *Saccharomyces* and *Kluveromyces*.

After duplication, one copy of many of the genes in a duplicated genome segment is lost. Once duplicate segments have been identified, comparisons between the two allow the gene composition of the common ancestor to be estimated (Fig. 2). Having done this, duplicated regions that are even more ancient become apparent — pairs of genes and gene regions that were not initially identified because too many puzzle pieces were missing. At the same time, it is possible to identify the pattern and relative rate of gene loss. Repeating their evolutionary analysis for the newly identified duplicated segments, Bowers *et al.* were able to identify a more ancestral duplication event early in the evolution of the flowering plants, after the ancestor of cotton and *Arabidopsis* (which are both dicotyledonous plants) diverged from the ancestor of rice and maize (which are monocotyledons). Another round of analyses revealed a duplication that was still more ancient, possibly occurring before the origin of the seed plants.

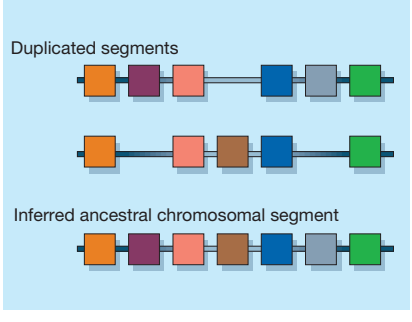

Figure 2 **Duplicated chromosomal segments, showing some gene pairs. This pattern of duplication suggests that all seven genes may have been present and in the same order in the common ancestor.**

A historian, trying to dissect cause and effect, needs to know the relative times of battles and treaties. Similarly, the biologist needs to know the relative times of gene duplications, speciation events, major species diversifications, and events of Earth history. Approaches that involve the construction of evolutionary trees are designed specifically to assess relative time. Incorporating such an approach into future genome studies will undoubtedly lead to a clearer picture of the role of gene and genome duplication in the evolutionary process. By increasingly dense sampling of evolutionary trees, even without complete genome sequences for every species, it is possible to distinguish single-gene duplications from whole-genome duplication. So the approach holds the promise of dissecting the dynamic processes by which genes and genomes evolve. ■

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Nonlinear dynamics

Synchronization from chaos

Peter Ashwin

It isn't easy to create a semblance of order in interconnected dynamical systems. But a mathematical tool could be the means to synchronize systems more effectively — and keep chaos at bay.

Chaos and control are often seen as opposite poles of the spectrum. But the theory of how to control dynamical chaos is evolving, and, in *Physical Review Letters*, Wei, Zhan and Lai[1] present a welcome contribution.

Chaos is a feature in all sciences: from lasers and meteorological systems, to chemical reactions (such as the Belouzov–Zhabotinski reaction) and the biology of living organisms. In most deterministic dynamical systems that display chaotic behaviour, selecting the initial conditions carefully can drive the system along a trajectory towards much simpler dynamics, such as equilibrium or periodic behaviour. But sensitive dependence on initial conditions — the well-known 'butterfly effect' — and the effects of noise in the system mean that in practice this is not so easy to do.

The aim of chaos control is to be able to perturb chaotic systems so as to 'remove' or at least 'control' the chaos. For example, in a spatially extended system, the aim may be to achieve regular temporal and/or spatial behaviour. Techniques introduced[2,3] and developed by several researchers over the past decade have sought to make unstable behaviour robust against both noise and uncertainties in initial conditions by stabilizing the system (using feedback[3], for instance) close to dynamically unstable trajectories. These techniques have been very successful in controlling chaos, at least for low-dimensional systems.

Synchronization is a good example of a chaos-control problem: synchronizing an array of coupled (interdependent) systems — such as the coherent power-output from an array of lasers — is of interest for technological applications. In biology, synchronization of coupled systems is a commonly used model[4], and the presence, absence or degree of synchronization can be an important part of the function or dysfunction of a biological system. For example, epileptic seizures are associated with a state of the brain in which too many neurons are synchronized for the brain to function correctly.

In the simplest case, synchronization of two identical coupled systems (such as periodic oscillators) can be achieved through their coupling as long as it is strong enough to overcome the divergence of trajectories within either individual system. The required strength is indicated by the most positive Lyapunov exponent of the system: a Lyapunov exponent is an exponential rate of convergence or divergence of trajectories of a dynamical system, and the most positive Lyapunov exponent measures the fastest possible rate of divergence of trajectories. In particular, the fact that the individual systems have chaotic dynamics before they are coupled together means that the most positive Lyapunov exponent is greater than zero, and there is always a threshold below which synchronization cannot be achieved.

Synchronization in more general arrays can be done similarly, although with local coupling this can only be achieved with a

coupling strength that grows with system size. This synchronization can be achieved without forcing the dynamics to become, for example, periodic. Hence, the problem of spatial control of coupled dynamics, although it still involves stabilizing dynamics that are inherently unstable, is easier to achieve than control of chaotic into simple dynamics. Control of synchronization can usually be achieved by careful design of the coupling, rather than resorting to feedback techniques. What then remains is to try to minimize the level of coupling required to achieve synchronization.

This is the problem that Wei, Zhan and Lai[1] have tackled. They have come up with a novel way of reducing the necessary coupling in an array by using wavelet decomposition of the matrix of coupling coefficients. Wavelets are mathematical functions that have been developed over the past decade or so as a powerful tool for signal-processing and numerical analysis. Wavelet analysis involves reducing a signal into a series of coefficients that can be manipulated, analysed or used to reconstruct the signal. Wei *et al.* make a small change to the low-frequency components in the wavelet-transformed matrix, before applying an inverse transform to obtain a modified coupling matrix. This turns out to be an efficient strategy for achieving synchronization at much lower coupling strengths.

Wei *et al.* test their method by synchronizing a ring of coupled Lorenz systems. The Lorenz system is a set of three nonlinear differential equations showing chaotic behaviour. In this proof-of-principle, a ring of Lorenz systems are coupled together linearly, their relations to each other represented by a matrix of coupling coefficients. A small change in this matrix (less than 2% for 64 coupled systems), through the wavelet transform, produces a much lower threshold of coupling to achieve synchronization. The authors show that their technique is robust even if the symmetry of nearest-neighbour coupling is broken.

It will be interesting to see if this method can be extended to more general arrays of coupled systems, to better understand control of spatial patterns. It may be that the work by Wei *et al.*[1] will suggest new techniques and structures for the design of local and global coupling in such systems. ■

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Neurobiology

Ballads of a protein quartet

Mark P. Mattson

The fate of neurons in the developing brain and in Alzheimer's disease may lie with a four-protein complex that regulates the cleavage of two molecules spanning the cell membrane. The role of each protein is now being unveiled.

Scientific discoveries often originate in surprising places. Some years ago, for instance, researchers looking at how the brain develops received help from an unexpected quarter: studies of patients with Alzheimer's disease. This disease is characterized in part by the abnormal accumulation, in the brain, of a protein called amyloid β-peptide (Aβ), which is a fragment of a larger protein, the amyloid precursor protein (APP), that sits across the outer membrane of nerve cells. Two enzymatic activities are involved in precisely snipping APP to produce Aβ, which is then shed into the brain. Curiously, one of these activities — dubbed γ-secretase[1] — was later discovered also to cleave Notch, a receptor protein that lies on the cell surface, and thereby to affect the way in which Notch regulates gene expression during normal development[2]. On page 438 of this issue, Takasugi and colleagues[3] add to our understanding of how APP and Notch are processed. Using genes and cells from flies and humans, and the powerful new technology of RNA interference, these authors establish specific roles for four different proteins underlying γ-secretase activity.

For many years, much of the research into Alzheimer's disease has concentrated on identifying and characterizing the protein (or proteins) that generate Aβ. In the first step of this process, APP is cleaved at a specific point by a so-called β-secretase activity; the protein responsible for this activity was identified some four years ago. Cleavage by the γ-secretase activity then produces Aβ — but here the molecules at fault have been harder to pin down. An early hint came from the finding that mutations in a gene encoding the presenilin-1 protein occur in several families with inherited Alzheimer's disease; it was quickly shown that these mutations cause increased cleavage of APP to produce Aβ. So presenilin-1 was assumed to be the γ-secretase.

A surprising link to brain development was then discovered when researchers knocked out the presenilin-1 gene in mice (reviewed in ref. 2). The animals died as embryos, and had severe defects in brain development that were indistinguishable from the defects in mice lacking Notch. This is because presenilin-1 is required not only to cleave APP and generate Aβ, but also to cleave Notch after Notch has detected and bound a partner protein. An intracellular fragment of Notch is then released, and regulates gene expression in the neuronal nucleus. It has been suggested[4] that an intracellular fragment of APP, generated by γ-secretase, likewise moves to the nucleus and regulates gene expression.

But it soon became clear that presenilin-1 cannot work alone to cleave APP and Notch, and a search began for other proteins that might be involved. APP and Notch have been highly conserved during evolution, which not only attests to their physiological importance, but also means that molecular-genetic analyses of fruitflies and worms can be used to investigate their cleavage. Such studies have found that four proteins seem to contribute to γ-secretase activity; these are presenilin-1, nicastrin, APH-1 and PEN-2 (Fig. 1, overleaf)[5–7]. It has just been shown that γ-secretase activity can be fully reconstituted with only these four proteins[8].

But what exactly do these proteins do? To begin to understand this, Takasugi and co-workers[3] first generated fruitfly cells that expressed different combinations of fruitfly nicastrin, APH-1 and PEN-2 and determined the effects on cleavage of presenilin-1 (this event having been previously associated with γ-secretase activity). They found that overexpression of APH-1 — or APH-1 plus nicastrin — stabilized the four-protein complex and simultaneously reduced presenilin-1 cleavage, suggesting that APH-1 inhibits the ability of γ-secretase to cleave any of its target proteins. They then showed that, indeed, APH-1 reduces the γ-secretase cleavage of APP as well.

To determine the role of PEN-2 in the γ-secretase quartet, the authors used RNA interference to target and degrade the messenger RNA encoding PEN-2, thereby reducing production of the protein, in fruitfly cells, mouse and human brain neurons, and human tumour cells. This resulted in decreased γ-secretase activity. Further experiments in which a fragment of APP was added confirmed that APH-1 inhibits, whereas PEN-2 promotes, the production of Aβ. These findings advance our understanding of an enzyme activity that is important in both brain development and Alzheimer's disease, and identify new protein targets for drugs to prevent or treat this disorder. But the results also raise new questions, and reveal further hurdles to treating Alzheimer's disease.

One general question is whether the