country in real vistas and artistic representation. It seems likely that this is a further example of that taste.

Reports have associated the new painting with the Emperor Nero (AD 54–68), whose lavish themed palace, the Golden House, was nearby. It has even been suggested that this is Rome before the destructive Great Fire of AD 64, which was blamed on Nero, and which made possible the building of his dream home by obliterating the earlier urban landscape. In fact, the painting is probably much later.

There are other reasons, though, to link it, at least impressionistically, with the urban ideal of Rome as the capital, and wonder, of the world. In the background is a large river crossed by a monumental bridge, not a common feature of ancient cities. And there are not many ancient cities that could claim such extremes of metropolitan grandeur — Alexandria, Antioch, Carthage; the list is not long. But the pictured city is hard to relate to the topography of ancient Rome, which did not acquire walls like this until the end of the third century AD. Neither does anything in the picture as it survives especially suggest the features we know of other great Roman cities. It is better to take it as a different kind of image — but one that is just as fascinating, for the insight it offers into how people of two millennia ago perceived urban environments that were as complex, socially and culturally, as any seen again in Europe before the nineteenth century. □

Nicholas Purcell is at St John's College, University of Oxford, Oxford OX1 3JP, UK.
e-mail: purcell@fyfield.sjc.ox.ac.uk

Developmental biology

Worlds in common through NF-κB

Cheryll Tickle

A transcription factor that regulates cell activity in the immune system and a human syndrome that affects face and limb development seem worlds apart. On pages 611 and 615 of this issue, however, Kanegae *et al.*[1] and Bushdid *et al.*[2] report an unsuspected role of NF-κB that brings these worlds together in the context of chick limb development.

NF-κB (or, to give it its full name, nuclear factor regulating expression of kappa light-chain immunoglobulin) is a well-known transcriptional regulator that was first identified in B cells[3]. Its activity is mediated by a family of molecules, including the product of the gene, c-*rel*. The two new papers[1,2] report that c-*rel* is expressed in cells at the tip of chick limb buds. When NF-κB activity is blocked, limb abnormalities, mostly truncations, are observed. This provides direct evidence that this intracellular signalling mechanism is necessary for vertebrate embryonic development. Members of the NF-κB family were already known to be homologous to the product of the *Drosophila* gene *Dorsal*[4], and this led to the identification of targets of NF-κB signalling in the chick limb. Last year, mutations in one of these targets, the *Twist* gene, were shown to be responsible for the human Saethre–Chotzen syndrome in which limb anomalies are found[5].

The region of undifferentiated mesoderm cells in the chick limb bud that expresses c-*rel*, and thus possesses NF-κB activity, is where patterning signals operate. This region is called the progress zone and remains at the tip of the bud as it grows out. As cells leave this zone, they form the series of structures along the long axis of the limb in succession — for example, first 'upper arm', then 'lower arm' and finally 'hand'. The current working hypothesis is that limb cells 'know' which structure to form by the length of time they spend in the progress zone[6].

Almost exactly 50 years ago, John Saunders[7] discovered that the thickened rim of the epithelial covering of the limb bud, the apical ectodermal ridge, is responsible for maintaining the progress zone. When the ridge is cut away, limb truncations result. The extent of truncation depends on the stage of limb development at which the ridge is removed, and ranges from almost complete absence of limb (ridge removed early) to just absence of the hand (ridge removed late). Truncations are the most consistent type of defect reported by Kanegae *et al.*[1] and Bushdid *et al.*[2] when NF-κB signalling is inhibited, although sometimes the limbs are also 'twisted'. Interactions between ridge and progress zone are reciprocal, and cells in the progress zone in turn maintain the ridge. So blocking NF-κB function may interfere either with the response of progress zone to ridge signalling or with progress zone signalling to the ridge.

The intimate knowledge of how NF-κB operates provided a neat way of demonstrating c-*rel* function in the chick limb. In unstimulated cells, NF-κB is sequestered in the cytoplasm by the inhibitory protein I-κB (Fig. 1a, overleaf). When the cell is stimulated, NF-κB is released and moves from cytoplasm to nucleus, where it binds to regulatory elements of target genes. Signalling can therefore be blocked by mutant forms of I-κB which do not release NF-κB. Such forms of I-κB, for example a form that cannot be phosphorylated and degraded, were expressed by Kanegae *et al.* in the developing chick limb using viruses, and this led to the limb truncations. Mice in which the gene encoding NF-κB has been knocked out

100 YEARS AGO

I send you a photograph of probably the most extraordinary heron's nest ever discovered in this or any other country. During a gale it was blown from the top of an elm tree in the heronry on Stoke Hall estate in Notts, the seat of Sir Henry Bromley, Bart. It is of unusual size, and almost exclusively composed of wire of varying lengths and thickness; the centre, or "cup," alone being composed of fine twigs, grasses and feathers. ... The other curious feature of the Stoke Hall phenomenon is that there is not, and never has been, any lack of ordinary building material, and that all the wire used must have been carried a great distance.

* * * * *

An interesting observation upon the development of a taste for honey by starlings is recorded by Mr. W. W. Smith in the *Entomologist* (April). In a previous note referring to some enemies of humble-bees in New Zealand, Mr. Smith stated that he had observed the newly-introduced starlings killing and conveying humble-bees to their nests to feed their young. ... this bird now frequents the flax-flats and sucks the honey from the richly mellifluous flowers. It appears probable that the eating of the humble-bee's honey-sac by the starlings developed, or is now developing, the taste for honey in these birds.
From *Nature* 7 April 1898.

50 YEARS AGO

In 1941 we published a theory which provided, among other things, an explanation of seasonal and latitude variations in the thickness of atmospheric ozone. From this theory we were able to predict ozone thicknesses in latitudes for which, as yet, there are no direct observations – for example, in polar regions. Furthermore we have shown that near the poles the ozone thickness should be practically zero soon after the winter solstice. Now routine measurements of ozone thickness, carried out by E. Tönsberg and K. L. Olsen in Tromsö, have shown values so low as 0.05cm. in December. It may be assumed that these occurrences are due to the movement of air masses from higher latitudes, so that the results afford good confirmation of our theoretical predictions.
From *Nature* 10 April 1948.

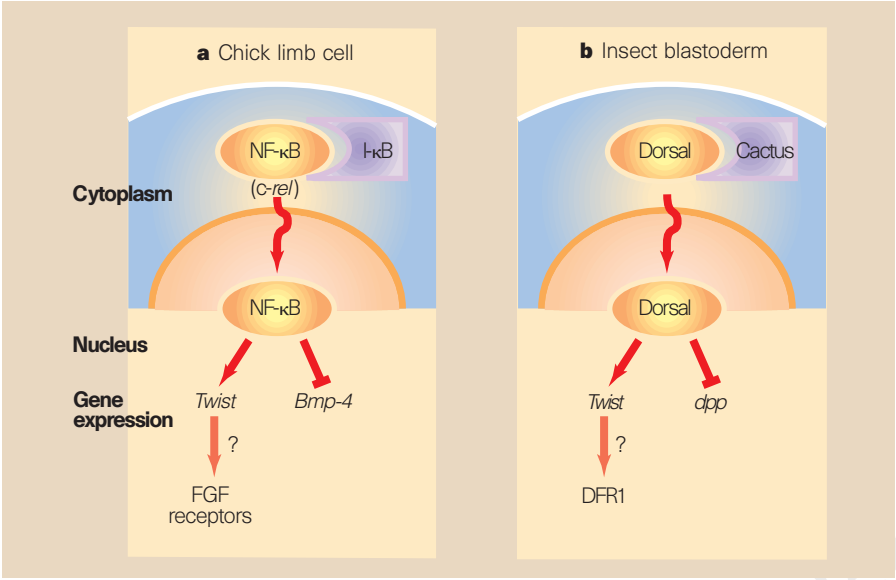


Figure 1 **Outline of a developmental pathway based on NF-κB signalling.** a, **Signalling through NF-κB in chick limb cells occurs by its release from I-κB and translocation to the nucleus where it regulates target genes (activation of *Twist* and repression of *Bmp-4*). Gene(s) encoding receptors for fibroblast growth factor (FGF) could lie downstream of *Twist*. These targets in the chick limb bud cells were identified by Kanegae *et al.*[1] and Bushdid *et al.*[2] by reference to known targets of NF-κB in *Drosophila*.** b, **In *Drosophila* blastoderm, signalling through Dorsal, a homologue of NF-κB, occurs by its release from Cactus and translocation to the nucleus, where it activates *Twist* and represses expression of *decapentaplegic* (*dpp*, of which *Bmp-2* and *Bmp-4* are vertebrate homologues). A *Drosophila* homologue of vertebrate FGF receptors (DFR1) appears to lie downstream of *Twist*, at least in the imaginal discs. A human connection comes from the finding[5] that mutations in the *Twist* gene cause Saethre–Chotzen syndrome, which is characterized by limb anomalies. For simplicity, NF-κB activity is represented here as a single entity, although it is known to act as a hetero- or homo-dimeric complex.**

develop normally, however, presumably because other NF-κB family members compensate for its absence[8].

Further dissection of the NF-κB signalling pathway in the chick limb was possible because of the extraordinary parallels between development in *Drosophila* and in vertebrates. NF-κB is homologous to the product of the *Drosophila* gene *Dorsal* — *Dorsal* signalling occurs by the same mechanism as NF-κB signalling, with Cactus being the homologue of I-κB (Fig. 1b)[9]. *Dorsal* is known to activate expression of a gene called *Twist* (encoding a regulatory helix–loop–helix protein), in the region of the insect body where mesoderm will form.

This led Kanegae *et al.*[1] and Bushdid *et al.*[2] to examine *Twist* expression in the chick limb, and they show that, when NF-κB signalling is blocked, *Twist* expression is reduced. Interestingly, early limb buds of *Twist*-null mouse embryos, which die about midway through gestation, have been reported to be stunted[10]. This then fits very nicely with the limb truncations obtained when NF-κB signalling is blocked. Another insight from *Drosophila* links *Twist* expression to apical ridge signalling. In *Drosophila*, a gene closely related to the genes encoding receptors for vertebrate fibroblast growth factor appears to be downstream of *Twist*[5]. Apical ridge signalling in the chick limb is known to be mediated by fibroblast growth factors. So *Twist* expression in the limb could be directly connected with the ability of cells in the progress zone to respond to ridge signals.

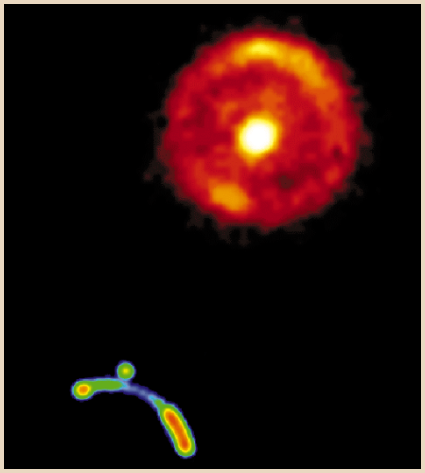
In *Drosophila*, *Dorsal* not only promotes *Twist* expression but also represses expression of *decapentaplegic* (*dpp*), which encodes a signalling molecule (Fig. 1b). Again, a parallel emerges in the chick limb. Bushdid *et al.*[2] show that blocking NF-κB signalling leads to increased expression of a vertebrate homologue of *dpp*, a gene encoding a bone morphogenetic protein, BMP-4. These proteins were originally named because of their ability to induce bone. They now appear to be multifunctional molecules, being implicated not only in skeletal

Extragalactic astronomy

A ring in truth

The orange bullseye is an image of two galaxies. One, at the centre, has stretched the image of the other into a ring — the first complete 'Einstein ring' ever seen. This is just one of many gravitational lenses collected in recent years, by a programme that aims to answer fundamental questions about the Universe's geometry and composition.

Einstein's theory of General Relativity predicts that light rays are curved by gravitational fields. The first confirmation of this effect came in 1919, when the Hyades star cluster was observed slightly out of place during a solar eclipse — a weak example of gravitational lensing. More interesting lenses occur where one distant galaxy or quasar appears to us in several distorted images, around the position of an intervening galaxy or galaxy cluster. More than 20 are known, including some partial Einstein rings, where the



lensed and the lensing objects are almost perfectly aligned.

Prompted by observations from the MERLIN array of radio telescopes, the Hubble Space Telescope has imaged this complete Einstein ring (L. J. King *et al.* *Mon. Not. R. Astron. Soc.* 295, L41–L44; 1998). The radio image, shown below Hubble's infrared image, isn't a complete ring because the radio-emitting part of the lensed galaxy is a little off-centre.

So how do lenses reveal the geometry of the Universe? It is a matter of statistics. The redshift distribution of lensed objects tells us what proportion of our lines of sight to distant regions are blocked by intervening galaxies. That is a function of the geometry of space-time, which in turn depends on the amount of matter present, and on the energy density of empty space — the 'cosmological constant', which Einstein introduced and then abandoned, but which is beginning to come into vogue again. By the end of this year, the team working with MERLIN hope to put the strictest limits yet on the cosmological constant.

Stephen Battersby

differentiation in the chick limb but also in positional signalling and programmed cell death[11].

The connection between NF-κB and *Twist* provides the satisfying link to Saethre–Chotzen syndrome. This human condition is characterized by craniofacial and limb anomalies, and the same developmental pathway probably operates in both regions of vertebrate embryos. At present, it is difficult to see just how alterations in *Twist* could lead to the specific anomalies in the limb (short digits and soft tissue webbing between digits). For although genes bring different worlds together, the challenge remains to understand how gene expression is translated into anatomy. □

Cheryll Tickle is in the Department of Anatomy and Developmental Biology, University College London, Medawar Building, Gower Street, London WC1E 6BT, UK.
e-mail: ucgcamt@ucl.ac.uk

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Computing

Parallel thinking

C. S. Calude and J. L. Casti

The computer seems to be the only commodity ever to become exponentially better as it gets cheaper. Its information handling capacity has grown at a rate ten million times faster than that of our nervous systems during the four billion years since life began on Earth. Yet the theory and technology of computing has rested for more than 50 years on the Turing-machine model of computation, which leads to many intractable or undecidable problems. Are there alternatives? This was the question addressed at a conference in January*, where three new models of computation were discussed: the DNA model, the quantum model and the reversible model.

DNA has a potentially gigantic memory capacity (in reasonable concentrations, a litre of DNA solution can store up to 10^{22} bits of information), and biochemical operations are massively parallel. So DNA has a built-in computational power. The familiar double helix of DNA arises by the bonding of two separate polymer chains, composed of the four DNA bases A, G, C and T. These obey the Watson–Crick complementarity rule: A bonds with T and C bonds with G. This restriction means that one DNA chain can pair with another chain only when their sequences of bases are complementary. Thus, fundamental information is available for free: knowing one member of a bond means automatically knowing the other.

The startling thing is that complementarity yields universality, in the Turing sense (A. Salomaa, Turku Univ.). Consider the set of all possible words (sequences) that can be obtained from two given words by shuffling them without changing the order of letters. For instance, shuffling AG and TC we get AGTC, ATCG, TCAG and TAGC. Then collect all shufflings of all pairs of complementary words into the so-called twin-shuffle language. There is a simple way to go from a DNA double strand to a word in the twin-shuffle language and back. Universality follows from the fact that any Turing computation can be performed by using an appropriate finite automaton to filter the (fixed) twin-shuffle language. So DNA computers could in theory perform any operation that digital computers can.

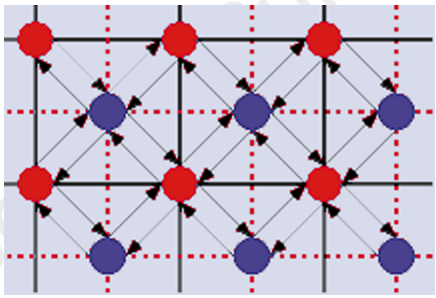

Figure 1 **The layout of a single cell of 'Flattop', an adiabatic (and therefore reversible) processor. It is based on the billiard-ball cellular automaton, in which logic values are modelled by the presence or absence of 'billiard balls' moving along paths in a grid. This scheme has now been realized, using a split-level charge-recovery logic circuit.**

It is a long way from theory to implementation, however. Biochemical operations are slow and prone to errors. The extraction of DNA strands containing a particular sequence is far from certain. Physical constraints, such as volume (performing the computation within a practical volume of DNA), time (some operations can take up to 100 minutes, at present) and energy (operations such as denaturing and annealing require heating or cooling) are difficult to control. But a new cloning readout procedure that overcomes some of these problems was described at the meeting. Using bacteriophage DNA rather than synthesized DNA to carry encoded solutions, operations such as removal, restriction and sorting can be performed by gel electrophoresis, and the result can be obtained in an error-resistant way by picking individual clones and sequencing their DNA (M. Amos, Liverpool Univ.).

Computers, in contrast to Turing machines, are physical devices: whatever they can or cannot do is determined by the laws of physics. Quantum effects, such as interference and entanglement, are especially important, because in the race for miniaturization, computers will inevitably use circuits approaching the level of atoms and photons. There are also certain algorithms that, in principle, can be solved by a quantum computer much more quickly than by a conventional one.

Not all quantum effects may be needed. Nonlinearity (to support quantum logic and ensure universality) and coherence (for the manipulation of coherent quantum superpositions) are necessary and, in principle, sufficient conditions for computation. Conventional devices under investigation for carrying out these operations include ion traps, high-finesse cavities for manipulating light and atoms using quantum electrodynamics, and molecular systems designed to compute using nuclear magnetic resonance. These last store quantum information in the states of quantum systems such as photons, atoms or nuclei, and realize quantum logic by semi-classical potentials such as microwave or laser fields. Unconventional ideas for quantum computation include fermionic quantum computers, bosonic computers (which use a Bose–Einstein condensate of photons, phonons or atoms), and architectures relying on anyons (whose nonlocal topological nature makes them intrinsically error-correcting and virtually immune to noise and interference).

The third strand of the meeting was reversibility. An operation is reversible if it can be undone; it is simply determinism looking backwards in time. Conventional computers are irreversible, and constantly discard information about their states. This limits their efficiency, as it increases the energy required to perform computations and involves the dissipation of heat. But since the laws of physics are reversible at a microscopic level (a given microstate can only be reached by a single path), it follows that irreversible operations and the accompanying production of entropy are in principle not necessary. In practice, reversible computations are likely to dissipate far less energy — but avoiding all entropy production may hurt other measures of performance, such as speed.

The world's first fully reversible universal computer was presented at the meeting (T. Knight, MIT). Working with a parallel architecture (Fig. 1), the machine can perform any computation using arbitrarily little energy per operation (ignoring leakage and power-

Unconventional Models of Computation, Univ. Auckland, New Zealand, 5–9 January 1998.