the sample remains). For the Invar alloys this increasing disorder is volume dependent and so leads to a decreasing volume, thereby compensating for the vibrational thermal expansion.

This study provides a microscopic explanation for an effect that has puzzled scientists for more than a century. It also paves the way for future work on this class of materials. As well as the Invar effect there is the anti-Invar effect, in which an exceptionally large thermal expansion is found. This effect could also be used profitably, for example to make actuators for micromachines. It is also recognized that all Invar alloys have compositions that are surprisingly close to having structural instabilities. For example, in Fe–Ni alloys with a nickel concentration below 32%, the crystal structure is no longer f.c.c. but body-centred cubic. It is likely that these issues will keep solid-state physicists busy for years to come. □

Peter Mohn is at the Center for Computational Materials Science, Vienna University of Technology, Getreidemarkt 9/158, A-1060 Vienna, Austria.
e-mail: phm@cms.tuwien.ac.at

1. van Schilfgaarde, M., Abrikosov, I. A. & Johansson, B. *Nature* **400,** 46–49 (1999).
2. Guillaume, C. E. *C. R. Acad. Sci.* **125,** 235–238 (1897).
3. Wassermann, E. F. in *The Invar Effect: Centennial Symposium* (ed. Wittenauer, J.) 51 (Minerals, Metals & Materials Society, 1997).
4. Weiss, R. *Proc. R. Soc. Lond.* **82,** 281–288 (1963).

Cell cycle

A snip separates sisters

Andrew Murray

A paper by Uhlmann *et al.*[1] on page 37 of this issue sheds light on one of the mysteries of cell division — how sister chromosomes separate from one another as cells divide. To transform itself into two genetically identical daughters, a cell must perform three reactions on its chromosomes (Fig. 1a). The sequence begins at a stage known as interphase, where each chromosome replicates to generate a pair of sister chromosomes. Next, cells enter mitosis (nuclear division), and the two sisters align to face in opposite directions on the segregation machinery, or mitotic spindle. Finally, at the end of mitosis, the sister chromosomes separate and move to opposite poles of the spindle.

This chromosomal dance depends on the physical linkage between the two sisters, which allows them to align correctly, but must then be dissolved so they can separate at the end of mitosis. Logic suggests that the linkage must be established during DNA replication and then persist until mitosis; the sisters are uniquely close to each other during the act of replication, making it easy to link one sister to another rather than to a non-sister. If the sisters were not linked during replication, this spatial distinction would rapidly disappear as they diffused apart from each other.

Looking at extreme cases reveals that the stability of sister linkage can vary over seven orders of magnitude. In a human oocyte, for example, the sisters must remain linked to each other from the end of DNA replication until the oocyte enters the meiotic divisions that will transform it into an unfertilized egg — an interval that can exceed 50 years. Failure of this linkage is an important cause of Down's syndrome. By contrast, during early divisions of the fruitfly embryo, the chromosomes must receive the signal to separate and dissolve their linkage in less than two minutes.

Until recently, two obstacles limited our understanding of sister-chromosome linkage: ignorance about how sister separation is triggered at the right stage of the cell cycle, and our inability to see individual chromosomes in yeasts (which have dominated genetic analysis of the cell cycle). The first obstacle was removed with the discovery that cleavage of mitotic cyclins is required for exit from mitosis. The enzyme that targets cyclins for cleavage, the anaphase-promoting complex, also triggers the destruction of unknown proteins, which hold sister chromosomes (also known as sister chromatids) together, possibly by acting as a physical glue between them[2]. The second obstacle disappeared with the development of methods to locate specific sequences in yeast nuclei, first by *in situ* hybridization on fixed cells[3,4] and, later, by localization of fluorescent DNA-binding proteins to segments of DNA in living cells[5].

With these tools in hand, geneticists looked for mutants that perturb sister-chromosome linkage and separation. They identified a protein called Pds1 in budding yeast, or Cut2 in fission yeast, that had to be destroyed by the anaphase-promoting complex for the sisters to separate[6,7]. But Cut2/Pds1 does not bind to chromosomes, so it cannot be the glue that holds the sisters together. Instead, it controls the activity of another enzyme (Cut1 in fission yeast or Esp1 in budding yeast), which seems to cause separation of sister chromosomes. Initially Cut2/Pds1 helps to get Cut1/Esp1 into a form that will ultimately allow it to separate sisters, but the separating activity is not turned on until Cut2/Pds1 is cleaved and destroyed[7–9].

Further genetic screens identified proteins that bind to each other to form the cohesin complex, so named because sister chromosomes separate prematurely when any of its members are inactivated[10–12]. Two subunits of this complex, Smc1 and Smc3, are members of a class of ATPases that can alter the three-dimensional path of DNA molecules in space and have been implicated in a wide range of large-scale chromosomal behaviours including chromosome condensation, sister chromosome linkage, recombination and dosage compensation (reviewed

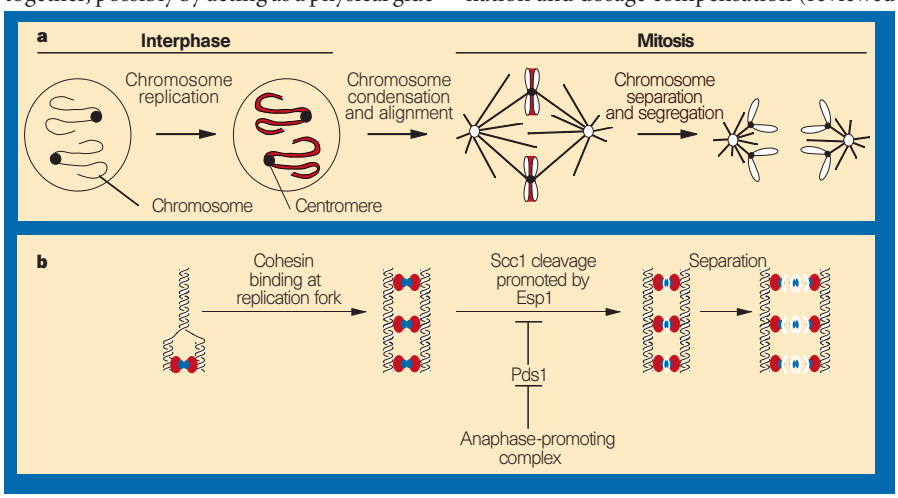

Figure 1 **Chromosomal events during cell division.** a, **Essential steps. During interphase, DNA replication generates two sister chromosomes, which are linked together by a molecular 'glue' (shown in red). The chromosomes condense and line up on the mitotic spindle, then the two sisters separate and migrate to opposite poles of the cell. This is followed by cell cleavage, yielding two genetically identical daughter cells.** b, **Molecular details. The different stages are aligned beneath the corresponding stages of the chromosome cycle. The cohesin complex (red) binds to the sister chromosomes during DNA replication. According to the results of Uhlmann *et al.*[1], the Scc1 subunit (blue) of the cohesin complex is cleaved at mitosis. This reaction is promoted by Esp1 which, in turn, is freed up to do this job through destruction of another protein called Pds1 by the anaphase-promoting complex. Cleavage of the cohesin complex allows the sister chromosomes to separate, and cell division to proceed.**

in ref. 13). The other proteins in the cohesin complex lack any known enzymatic activity, but are required for the complex to form and to bind to DNA. One of these subunits, Scc1 (also called Mcd1), dissociates when the sister chromosomes separate[10,11], but only if Esp1 is active. These results suggest that the cohesin complex holds the sisters together, and that its removal from the chromosomes triggers sister separation[9]. The complex can establish this linkage only during DNA replication, possibly owing to activities that travel with the replication fork[12,14].

These studies set the stage for the work of Uhlmann and colleagues[1], who used a mixture of biochemistry and genetics to show that sister separation requires cleavage of Scc1. The biochemical analysis relied on extractology — the study of complex reactions in crude, but concentrated, cell extracts that can be manipulated by the addition or subtraction of individual proteins. When Uhlmann *et al.* added chromatin to such an extract, the Scc1 was cleaved into three fragments and it dissociated from the chromatin. The authors found that this reaction requires Esp1 and is inhibited by Pds1, reflecting the requirements for sister separation *in vivo*.

Is cleavage a cause or a consequence of sister separation? To answer this critical question, Uhlmann *et al.* mapped the cleavage sites, then made mutations that blocked them and reintroduced the mutant gene into cells. The results were dramatic. Although the mutant Scc1 protein established sister-chromosome linkage during DNA replication, it did not leave the chromosomes during mitosis, and the cells died because the linkage between the sisters was not dissolved. So, two different sorts of proteolysis are needed to initiate sister separation. The first is activation of the anaphase-promoting complex, which leads to the wholesale destruction of Pds1. This, in turn, frees Esp1 to introduce two surgical snips in Scc1, thereby destroying the cohesin complex (Fig. 1b).

Other studies indicate that changes in the cohesin subunits are responsible for the difference between chromosome segregation in mitosis and meiosis. In mitosis, the sisters separate their arms and centromeres (the specialized region that attaches them to the spindle) at the same time. But in meiosis, the arms separate in the first division whereas the centromeres separate in the second. In fission yeast, delayed separation of the centromeres can be induced by replacing components of the mitotic cohesion complex with variants that are made only during meiosis. This result indicates that a change in a single chromosomal protein may be enough to cause the altered pattern of chromosome segregation that is responsible for sexual reproduction (Y. Watanabe and P. Nurse, personal communication).

So, have we finally identified the physical glue that holds the sisters together? And is Esp1 the protease that destroys it? The answer to both questions is a resounding 'maybe'. We cannot exclude the possibility that the cohesin complex regulates the stability of some other, more fundamental linkage. Support for this possibility comes from studies of frog egg extracts, in which the cohesin complex helps to set up sister linkage, but leaves the chromosomes as they enter mitosis — well before the sisters separate[15]. Moreover, sequence gazing suggests that Esp1 is unlikely to cleave Scc1, because it lacks homology to any known protease. The answers probably lie beyond the realms of genetics and extractology, but the questions should stimulate biochemists to roll up their sleeves and dissect the reactions that promote cell reproduction by abolishing chromosomal sisterhood. □

Andrew Murray is in the Department of Physiology, University of California, 513 Parnassus Avenue, San Francisco, California 94143-0444, USA.
e-mail: amurray@socrates.ucsf.edu

1. Uhlmann, F., Lottspeich, F. & Nasmyth, K. *Nature* **400,** 37–42 (1999).
2. Holloway, S. L., Glotzer, M., King, R. W. & Murray, A. W. *Cell* **73,** 1393–1402 (1993).
3. Uzawa, S. & Yanagida, M. *J. Cell Sci.* **101,** 267–275 (1992).
4. Guacci, V., Hogan, E. & Koshland, D. *J. Cell Biol.* **125,** 517–530 (1994).
5. Straight, A. F., Belmont, A. S., Robinett, C. C. & Murray, A. W. *Curr. Biol.* **6,** 1599–1608 (1996).
6. Yamamoto, Y. A., Guacci, V. & Koshland, D. *J. Cell Biol.* **133,** 99–110 (1996).
7. Funabiki, H. *et al. Nature* **381,** 438–441 (1996).
8. Kumada, K. *et al. Curr. Biol.* **8,** 633–641 (1998).
9. Ciosk, R. *et al. Cell* **93,** 1067–1076 (1998).
10. Guacci, V., Koshland, D. & Strunnikov, A. *Cell* **91,** 47–57 (1997).
11. Michaelis, C., Ciosk, R. & Nasmyth, K. *Cell* **91,** 35–45 (1997).
12. Toth, A. *et al. Genes Dev.* **13,** 320–333 (1999).
13. Hirano, T. *Genes Dev.* **13,** 11–19 (1999).
14. Uhlmann, F. & Nasmyth, K. *Curr. Biol.* **8,** 1095–1101 (1998).
15. Losada, A., Hirano, M. & Hirano, T. *Genes Dev.* **12,** 1986–1997 (1998).

Particle physics

And you're glue

Frank Wilczek

It's a widely believed half-truth that protons and neutrons are made out of quarks. Actually, physicists are increasingly discovering that it's considerably less than half the truth. The modern theory of the strong force, which binds quarks inside protons and neutrons, and these particles in turn to make atomic nuclei, is quantum chromodynamics (QCD). The other ingredients of QCD, the colour gluons, were once conceived as mere paste that somehow links together more substantial stuff (their name reflects this). No longer. On closer inspection, the quarks appear as the showier, but gluons as the weightier and more dynamic, constituents of matter. Definitive images[1] from a microscope capable of looking inside protons, the HERA accelerator in Hamburg, Germany, reveal as well that there is more to gluons than meets the eye.

To understand these evolving views, you must consider how one goes about looking inside a proton, to 'see' what it is made of. An ordinary microscope, using ordinary light, is woefully inadequate, because the wavelength of light is about one billion times larger than the size of the proton. Even fancy electron or scanning tunnelling microscopes can barely resolve single atoms, and fall far short of seeing the nucleus inside. The right tool for the job is a high-energy accelerator. They produce virtual photons of very short wavelength (and lifetime), that can be used to take snapshots of the proton's interior (Box 1, overleaf).

There's a catch, however, to this seemingly straightforward procedure. You get to see only what the virtual photon allows you to see. And because the photons couple only to electrically charged particles, constituents of

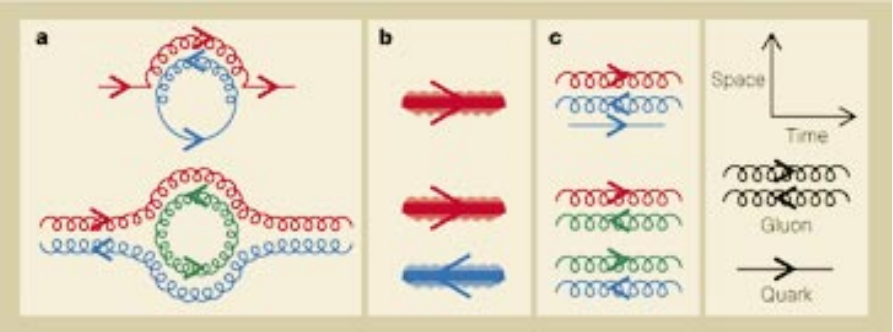

Figure 1 **What once appeared as fuzzy quarks or gluons are clearly imaged in a faster exposure, which reveals additional gluons.** a, **The flow of colour charge around a quark (top) or gluon (bottom) in time. Quarks carry a single unit of colour charge: red, blue or green. Gluons carry both positive and negative units of colour charge.** b, **Average views of the same quark and gluon with coarse time resolution** c, **In each case, a sharper-resolution view of the central time interval reveals the existence of an additional gluon.**