quency of the two states. In this case, the emission persists as long as the phase relation between the two excited states is preserved.

In real systems, however, coherence is lost because of processes such as collisions between electrons and interaction with lattice vibrations with a characteristic dephasing time. The important difference between previous coherent population control experiments in semiconductors (*9*) and the experiments presented by Bonadeo *et al.* (*1*) is that the dephasing time is much longer in a single dot (40 ps) than in bulk semiconductors (< 1 ps). The consequence is that a practically complete destruction of the population created by the first pulse is possible in a single quantum dot, whereas a destruction no better than 70% was achievable in the bulk material (*9*).

The feasibility of coherent control in a single quantum dot opens new perspectives for the use of quantum dots as quantum logic units for optical computing. Indeed, coherent control can be used to prepare the quantum dot in a target wave function that can be addressed optically. Multistate logic units could be achieved by the use of more than two confined states. Recent advances in quantum computation theory show that a chain of such quantum logic gates could perform sophisticated quantum computing operations such as factorization of large integer numbers in a much more efficient way than conventional two-state logic computers (*10*). The challenge now faced by scientists is to develop coherent control schemes useful for such applications. Moreover, one prerequisite for a practical quantum logic gate is a long decoherence time. In atoms, decoherence times as long as a few microseconds have been observed (*10*). Quantum dots, being solid-state systems, are technologically more practical than atoms, but much longer dephasing times still have to be achieved.

References and Notes

1. N. H. Bonadeo, J. Erland, D. Gammon, D. G. Steel, *Science* **282**, 1473 (1998).
2. For a recent review, see the special issue on Semiconductor Quantum Dots in *MRS Bull.* **23**, 15 (1998).
3. J. Y. Marzin, J.-M. Gérard, A. Izraël, D. Barrier, G. Bastard, *Phys. Rev. Lett.* **73**, 716 (1994).
4. S. Tarucha, D. G. Austing, T. Honda, R. J. van der Hage, L. P. Kouwenhoven, *ibid.* **77**, 3613 (1996).
5. S. M. Cronenwett *et al.*, *Science* **281**, 540 (1998).
6. K. Brunner *et al.*, *Phys. Rev. Lett.* **73**, 1138 (1994).
7. H. G. Roskos *et al.*, *ibid.* **68**, 2216 (1992).
8. A. Bonvalet *et al.*, *ibid.* **76**, 4392 (1996).
9. A. P. Heberle, J. J. Baumberg, K. Köhler, *ibid.* **75**, 2598 (1995).
10. A. Ekert and R. Jozsa, *Rev. Mod. Phys.* **68**, 733 (1996).

PERSPECTIVES: DNA REPLICATION

Bringing the Mountain to Mohammed

Richard Losick and Lucy Shapiro

All too often, molecular biologists have underestimated the flexibility of DNA. When it was first discovered that genes can be controlled by DNA elements located many kilobases away from the transcribed gene itself, such "enhancers" were thought to be entry sites for regulatory proteins. These proteins, it was imagined, would slide or otherwise send a signal down the DNA, depicted as a static and rigid rod, to the promoter of the gene. Only later did it emerge that the DNA, which is of course dynamic and flexible, forms a loop that directly juxtaposes enhancer-bound regulatory proteins with the promoter-bound transcription complex. Similarly, until recently, textbooks depicted the replication fork for DNA duplication with two DNA polymerases independently carrying out leading-strand and lagging-strand synthesis. Now we know that the two polymerases are locked together in a rigid replication machine and that the DNA template for the lagging strand loops out from the twin polymerases. Because of the enormous length of DNA, textbooks have also generally depicted the chromosome as stationary and the replication machinery as a kind of locomotive chugging along the DNA track. Now a report by Lemon and Grossman on page 1516 of this issue (*1*) provides fresh support for the opposite view—namely, that the replication machinery remains at a relatively fixed position and that the mountain of chromosomal DNA in the cell is threaded through this replication "factory" to emerge as two daughter chromosomes. Thus, the Mountain is brought to Mohammed rather than the other way around.

The concept that DNA replication takes place in immobile factories arose from four sets of experiments in eukaryotic cells (*2*). First, eukaryotic chromosomes have multiple origins of replication, and evidence showed that these origins often fire synchronously, as if the initiation of replication was somehow coordinated among origins that were widely spaced along the chromosome (*3*). Second, direct visualization by fluorescence microscopy revealed that replication is initiated at a relatively small number of discrete sites within the nucleus at which many origins are clustered (*4*). Third, these sites were shown to contain the protein machinery for DNA replication (*2*). Finally, and most telling, time-lapse experiments with pulse-labeled DNA revealed a punctate pattern of DNA synthesis in the nucleus and the extrusion of newly duplicated DNA from the sites of replication (*5*). Apparently, DNA is spooled through stationary replication factories during the process of DNA duplication. Berezney and colleagues (*6*) have recently extended this analysis to demonstrate the existence of distinct factories for transcription as well as replication, the subject of a recent Perspective by Cook (*6*).

A formidable challenge to proving that DNA is indeed threaded through immobile replication factories is the immense complexity of the process of DNA duplication in eukaryotic cells. During the S phase of the cell cycle, the nucleus contains more than 100 putative factories, and each factory contains as many as 300 replication forks (*3*). Hence, it is difficult to determine the position of individual factories relative to the architecture of the nucleus and therefore to be certain that the factories remain stationary and that DNA is spooled through them. Confidence in the factory model would be much higher if it were possible to visualize single replication forks and to monitor their location relative to cellular landmarks. Now Lemon and Grossman (*1*) have done just that through their discovery of what appears to be replication factories in the bacterium *Bacillus subtilis*.

Bacteria, which lack nuclei, have traditionally been viewed as vessels with proteins diffusing freely within an amorphous cytoplasm. Recent applications of electron and fluorescence microscopy, however, have revealed that many proteins in bacteria have distinct subcellular addresses (*7*). Furthermore, the prokaryotic chromosome is oriented in a specific way in bacteria, and bacteria may have a "mitotic apparatus" that is responsible for chromosome segregation during the

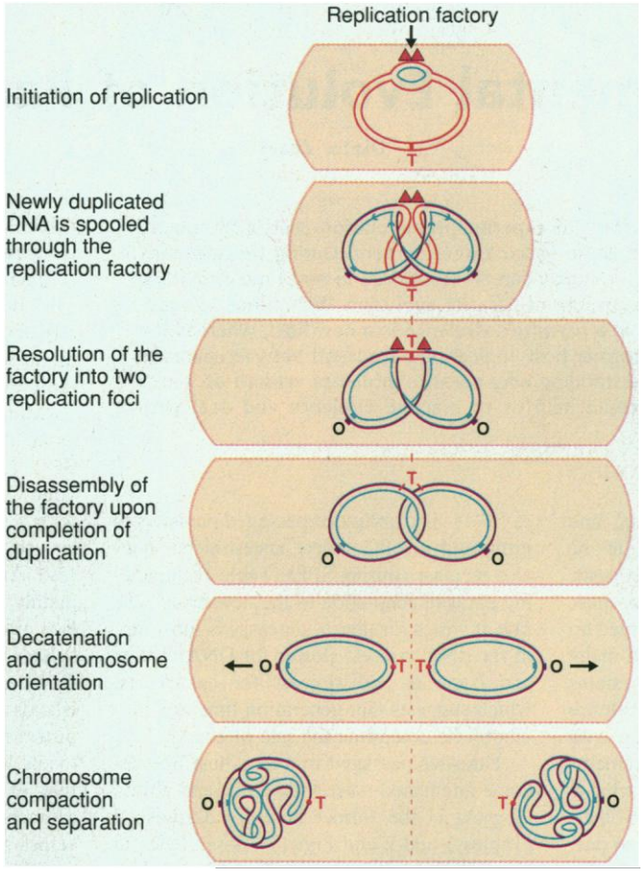
R. Losick is in the Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA 02138, USA. E-mail: losick@biosun.harvard.edu. L. Shapiro is in the Department of Developmental Biology, Stanford University School of Medicine, Stanford, CA 94305, USA.

cell cycle (*8*). These studies have shown that, after duplication, the replication origin regions rapidly move apart toward opposite poles of the cell. But where does DNA replication take place in bacteria? Using fusions of green fluorescent protein to the DNA polymerase (PolC) responsible for DNA replication as well as to two other components of the replication machine, Lemon and Grossman (*1*) have discovered that all three proteins are present as discrete foci in living cells. Moreover, these foci are located at or near the center of the cell even though the chromosome largely fills the cell (remember that bacteria do not have a nucleus). The clear inference from these findings is that the foci correspond to replication forks and that replication takes place in relatively stationary factories with the chromosome threaded through the factory.

What is the evidence that these foci correspond to replication forks? The bacterial chromosome, which is a circle, is replicated bidirectionally at two replication forks that originate from a single origin. Thus, the region of the chromosome containing the origin (O) replicates first, and the terminus region (T), about 180° away, is replicated last (see the figure). These constraints pose a problem for rapidly growing bacteria because the length of the cell cycle under optimal growth conditions is shorter than the time it takes for the replication forks to duplicate the entire chromosome. Under rapid growth conditions, bacteria solve this problem by initiating a second or even a third round of DNA replication before the first round of replication is complete. Thus, rapidly growing cells have multiple replication forks, whereas slowly growing cells have only two. Strikingly, the authors (*1*) found that most cells had only one or two fluorescent foci under conditions of very slow growth but as many as four foci under conditions of more rapid growth. This correlation between growth rate and the number of foci fits with the view that the foci are indeed the sites of DNA replication.

What is perhaps most astonishing about this work is that Lemon and Grossman (*1*) could visualize DNA polymerase at the replication forks at all. A single replication fork should contain only a single replication machine, which should consist of only two PolC molecules, one for the leading strand and one for the lagging strand. The two replication forks required for bidirectional replication (see the figure) would be expected to have only four PolC molecules, a small number to expect to be able to be visualized by fluorescence microscopy. Perhaps, as suggested by the authors (*1*), additional DNA polymerase molecules congregate near replication forks where they are poised to repair mismatches created by errors in replication.

What do these new findings tell us about the nature of the motor that drives chromosomes apart in bacteria? Eukaryotic cells have a conspicuous spindle apparatus that is responsible for segregating homologous chromosomes during mitosis, but the nature of the mitotic motor in bacteria is mysterious. It is known that bacteria have proteins that are responsible for chromosome condensation and that are crucial for the fidelity of chromosome segregation. But the nature of the engine that drives newly duplicated replication origins toward opposite poles of the cell remains elusive. The discovery of apparent replication factories located near the cell center raises the intriguing possibility that the process of DNA replication itself might contribute to the force required for segregation (*1*). As has been recently shown by time-lapse fluorescence microscopy, however, the segregation of chromosomes may not be a gradual, linear process (*9*). Rather, the newly duplicated origin regions of the chromosome sometimes appear to jump apart toward opposite poles of the cell before division. Thus, chromosome segregation may be composed of multiple stages: First, newly replicated DNA is spooled through a replication machine, and topological constraints force the new chromosomal regions apart. A second stage involving a possible "mitotic" apparatus might help to pull or push the newly replicated chromosomes to the poles. Finally, the daughter chromosomes undergo compaction (*10*), completing their separation from each other before cell division.



Duplicating bacterial DNA. Diagram of a replicating chromosome spooled through a stationary replication factory. The topologically complex chromosome is depicted in a simplified manner to illustrate movement of DNA during the cell cycle.

The findings of Lemon and Grossman (*1*) raise many fascinating questions. What anchors the replication factories near the middle of the cell, and what signals delocalization at the completion of replication? How many DNA polymerases are present near the replication fork? Is the energy from DNA synthesis harnessed for chromosome segregation?

References and Notes

1. K. P. Lemon and A. D. Grossman, *Science* **282**, 1516 (1998).
2. Reviewed by J. Newport and H. Yan, *Curr. Opin. Cell Biol.* **8**, 365 (1996).
3. J. A. Huberman and A. D. Riggs, *J. Mol. Biol.* **32**, 327 (1968).
4. J. Mills *et al.*, *J. Cell Sci.* **94**, 471 (1989).
5. P. Hozák, A. B. Hassan, D. A. Jackson, P. R. Cook, *Cell* **73**, 361 (1993).
6. X. Wei *et al.*, *Science* **281**, 1502 (1998); P. Cook, *ibid.*, p. 1466.
7. L. Shapiro and R. Losick, *ibid.* **276**, 712 (1997).
8. P. Glaser *et al.*, *Genes Dev.* **11**, 1160 (1997); P. J. Lewis and J. Errington, *Mol. Microbiol.* **25**, 945 (1997); D. C.-H. Lin, P. A. Levin, A. D. Grossman, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 4721 (1997); G. S. Gordon *et al.*, *Cell* **90**, 1113 (1997); D. A. Mohl and J. W. Gober, *ibid.* **88**, 675 (1997); C. D. Webb *et al.*, *ibid.*, p. 667; D. C.-H. Lin and A. D. Grossman, *ibid.* **92**, 675 (1998); H. Niki and S. Hiraga, *Genes Dev.* **12**, 1036 (1998); A. A. Teleman *et al.*, *Curr. Biol.* **8**, 1102 (1998).
9. C. D. Webb *et al.*, *Mol. Microbiol.* **28**, 883 (1998).
10. R. A. Britton, D. C.-H. Lin, A. D. Grossman, *Genes Dev.* **12**, 1254 (1998); S. Moriya *et al.*, *Mol. Microbiol.* **29**, 179 (1998).