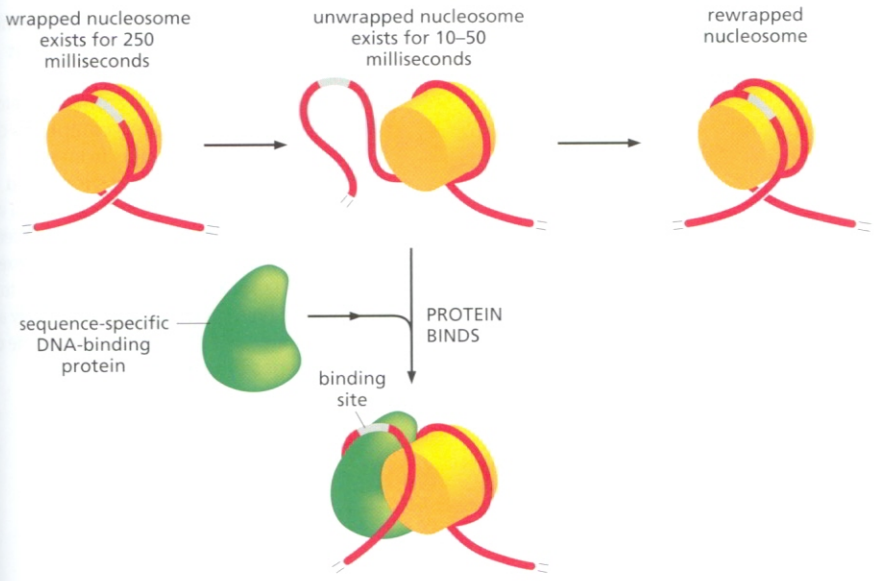



**Figure 4–28 Dynamic nucleosomes.** Kinetic measurements show that the DNA in an isolated nucleosome is surprisingly dynamic, rapidly uncoiling and then rewrapping around its nucleosome core. As indicated, this makes most of its bound DNA sequence accessible to other DNA-binding proteins. (Data from G. Li and J. Widom, *Nat. Struct. Mol. Biol.* 11:763–769, 2004. With permission from Macmillan Publishers Ltd.)

## Nucleosomes Have a Dynamic Structure, and Are Frequently Subjected to Changes Catalyzed by ATP-Dependent Chromatin-Remodeling Complexes

For many years biologists thought that, once formed in a particular position on DNA, a nucleosome remains fixed in place because of the very tight association between its core histones and DNA. If true, this would pose problems for genetic readout mechanisms, which in principle require rapid access to many specific DNA sequences, as well as for the rapid passage of the DNA transcription and replication machinery through chromatin. But kinetic experiments show that the DNA in an isolated nucleosome unwraps from each end at rate of about 4 times per second, remaining exposed for 10 to 50 milliseconds before the partially unwrapped structure recloses. Thus, most of the DNA in an isolated nucleosome is in principle available for binding other proteins (**Figure 4–28**).

For the chromatin in a cell, a further loosening of DNA–histone contacts is clearly required, because eucaryotic cells contain a large variety of ATP-dependent *chromatin remodeling complexes*. The subunit in these complexes that hydrolyzes ATP is evolutionarily related to the DNA helicases (discussed in Chapter 5), and it binds both to the protein core of the nucleosome and to the double-stranded DNA that winds around it. By using the energy of ATP hydrolysis to move this DNA relative to the core, this subunit changes the structure of a nucleosome temporarily, making the DNA less tightly bound to the histone core. Through repeated cycles of ATP hydrolysis, the remodeling complexes can catalyze *nucleosome sliding*, and by pulling the nucleosome core along the DNA double helix in this way, they make the nucleosomal DNA available to other proteins in the cell (**Figure 4–29**). In addition, by cooperating with negatively

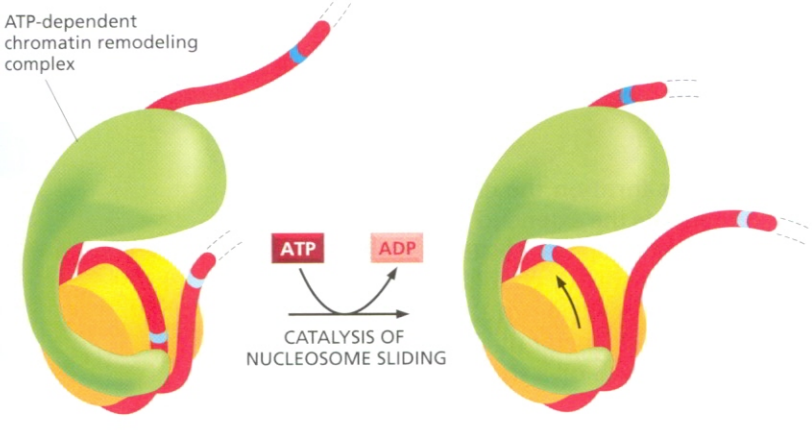



**Figure 4–29 The nucleosome sliding catalyzed by ATP-dependent chromatin remodeling complexes.** Using the energy of ATP hydrolysis, the remodeling complex is thought to push on the DNA of its bound nucleosome and loosen its attachment to the nucleosome core. Each cycle of ATP binding, ATP hydrolysis, and release of the ADP and $P_i$ products thereby moves the DNA with respect to the histone octamer in the direction of the arrow in this diagram. It requires many such cycles to produce the nucleosome sliding shown. (See also Figure 4–46B.)

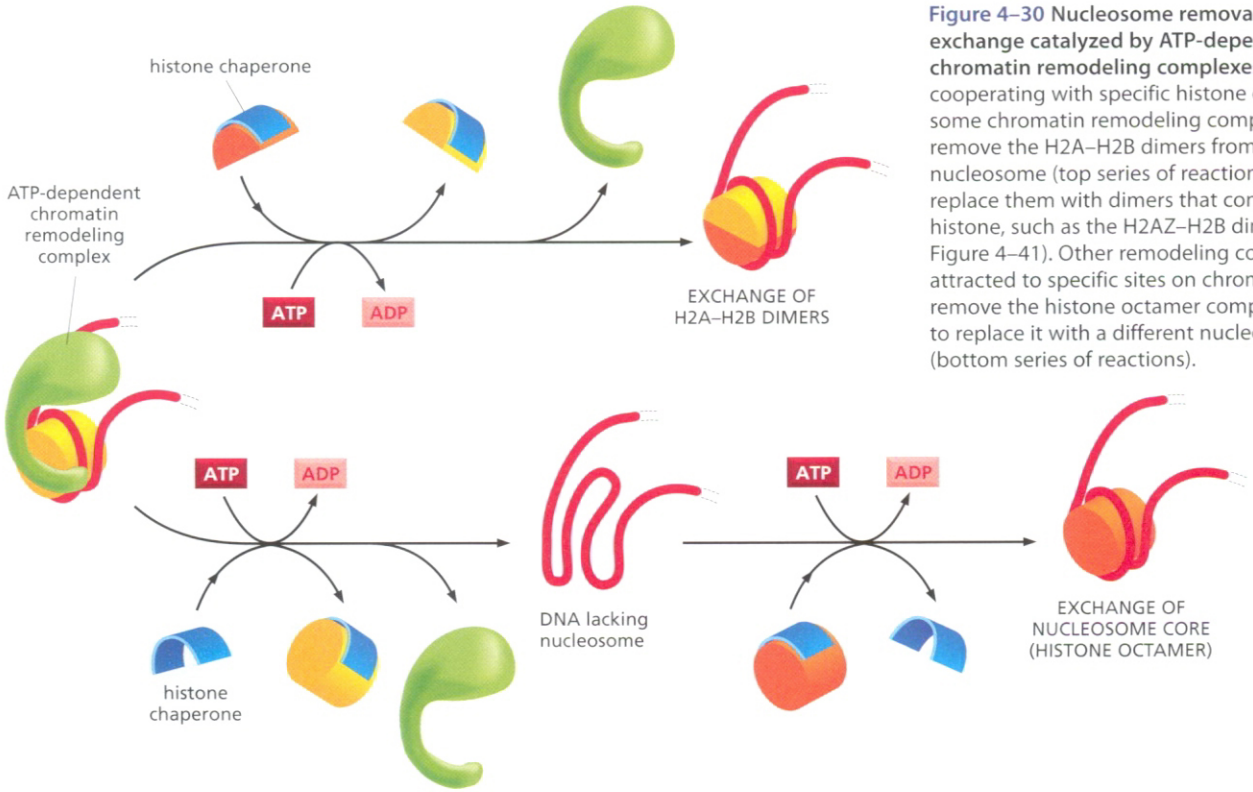



**Figure 4–30 Nucleosome removal and histone exchange catalyzed by ATP-dependent chromatin remodeling complexes.** By cooperating with specific histone chaperones, some chromatin remodeling complexes can remove the H2A–H2B dimers from a nucleosome (top series of reactions) and replace them with dimers that contain a variant histone, such as the H2AZ–H2B dimer (see Figure 4–41). Other remodeling complexes are attracted to specific sites on chromatin to remove the histone octamer completely and/or to replace it with a different nucleosome core (bottom series of reactions).

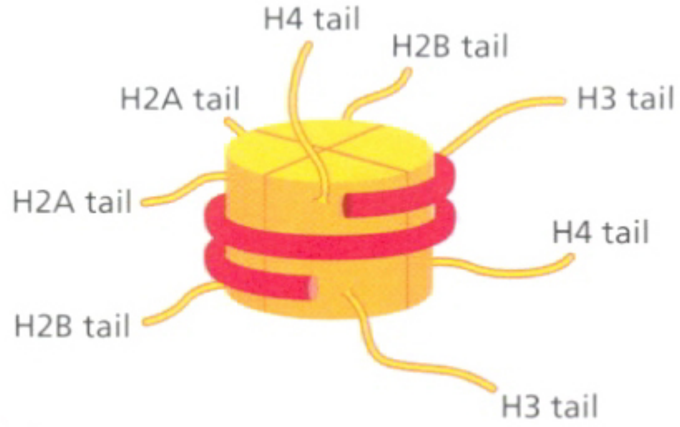
charged proteins that serve as histone chaperones, some remodeling complexes are able to remove either all or part of the nucleosome core from a nucleosome—catalyzing either an exchange of its H2A–H2B histones, or the complete removal of the octameric core from the DNA (**Figure 4–30**).

Cells contain dozens of different ATP-dependent chromatin remodeling complexes that are specialized for different roles. Most are large protein complexes that can contain 10 or more subunits. The activity of these complexes is carefully controlled by the cell. As genes are turned on and off, chromatin remodeling complexes are brought to specific regions of DNA where they act locally to influence chromatin structure (discussed in Chapter 7; see also Figure 4–46, below).

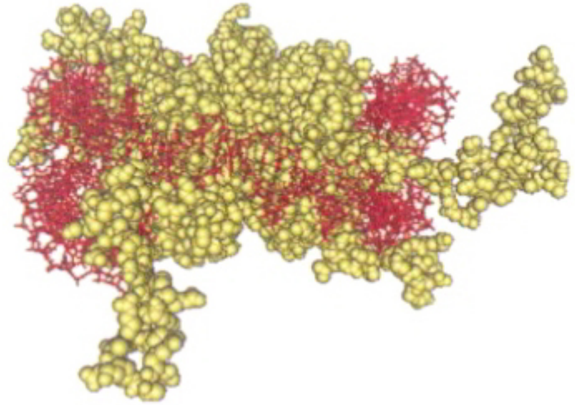
As pointed out previously, for most of the DNA sequences found in chromosomes, experiments show that a nucleosome can occupy any one of a number of positions relative to the DNA sequence. The most important influence on nucleosome positioning appears to be the presence of other tightly bound proteins on the DNA. Some bound proteins favor the formation of a nucleosome adjacent to them. Others create obstacles that force the nucleosomes to move to positions between them. The exact positions of nucleosomes along a stretch of DNA therefore depends mainly on the presence and nature of other proteins bound to the DNA. Due to the presence of ATP-dependent remodeling complexes, the arrangement of nucleosomes on DNA can be highly dynamic, changing rapidly according to the needs of the cell.

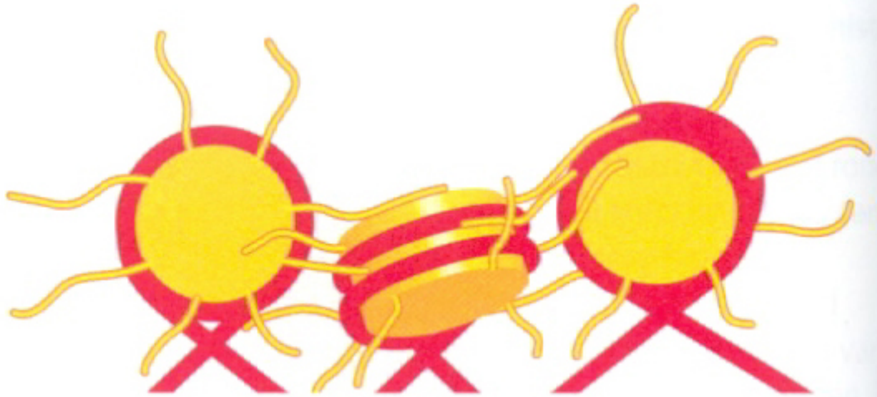
## Nucleosomes Are Usually Packed Together into a Compact Chromatin Fiber

Although enormously long strings of nucleosomes form on the chromosomal DNA, chromatin in a living cell probably rarely adopts the extended "beads on a string" form. Instead, the nucleosomes are packed on top of one another, generating regular arrays in which the DNA is even more highly condensed. Thus, when nuclei are very gently lysed onto an electron microscope grid, most of the chromatin is seen to be in the form of a fiber with a diameter of about 30 nm, which is considerably wider than chromatin in the "beads on a string" form (see Figure 4–22).

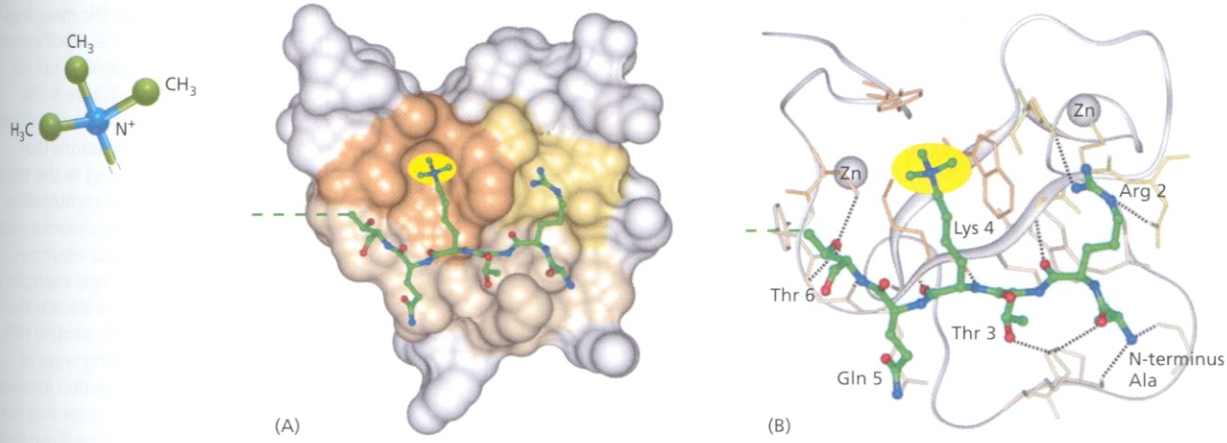

H4 tail
H2B tail
H2A tail
H3 tail
H2A tail
H4 tail
H2B tail
H3 tail

(A)





(B)




Many of the combinations appear to have a specific meaning for the cell because they determine how and when the DNA packaged in the nucleosomes is accessed, leading to the **histone code** hypothesis. For example, one type of marking signals that a stretch of chromatin has been newly replicated, another signals that the DNA in that chromatin has been damaged and needs repair, while many others signal when and how gene expression should take place. Small protein modules bind to specific marks, recognizing for example a trimethylated lysine 4 on histone H3 (**Figure 4–42**). These modules are thought to act in concert with other modules as part of a *code-reader complex*, so as to allow particular combinations of markings on chromatin to attract additional protein complexes that execute an appropriate biological function at the right time (**Figure 4–43**).

**Figure 4–42 How each mark on a nucleosome is read.** The structure of a protein module that specifically recognizes histone H3 trimethylated on lysine 4 is shown. (A) Space-filling model of an ING PHD domain bound to a histone tail (*green*, with the trimethyl group highlighted in *yellow*). (B) A ribbon model showing how the N-terminal six amino acids in the H3 tail are recognized. The *dashed lines* represent hydrogen bonds. This is one of many PHD domains that recognize methylated lysines on histones; different domains bind tightly to lysines located at different positions, and they can discriminate between a mono-, di-, and tri-methylated lysine. In a similar way, other small protein modules recognize specific histone side chains that have been marked with acetyl groups, phosphate groups, and so on. (Adapted from P.V. Pena et al., *Nature* 442:100–103, 2006. With permission from Macmillan Publishers Ltd.)

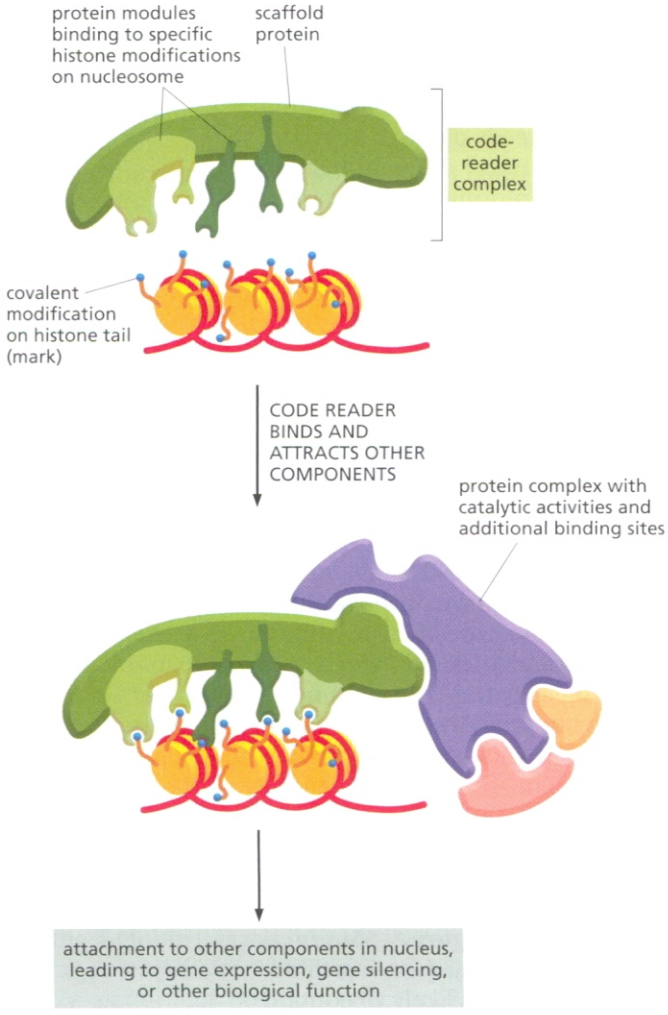



**Figure 4–43 Schematic diagram showing how the histone code could be read by a code-reader complex.** A large protein complex that contains a series of protein modules, each of which recognizes a specific histone mark, is schematically illustrated *(green)*. This "code-reader complex" will bind tightly only to a region of chromatin that contains several of the different histone marks that it recognizes. Therefore, only a specific combination of marks will cause the complex to bind to chromatin and attract additional protein complexes *(purple)* that catalyze a biological function.