# Holliday Model

All DNA is recombinant DNA. Genetic exchange works constantly to blend and rearrange chromosomes, most obviously during meiosis, when homologous chromosomes pair before the first nuclear division. During this pairing, genetic exchange between the chromosomes occurs. This exchange, classically termed crossing over, is one of the results of homologous recombination. Recombination involves the physical exchange of DNA sequences between the chromosomes. The frequency of crossing over between two genes on the same chromosome depends on the physical distance between these genes, with long distances giving the highest frequencies of exchange. Many of the popular models of crossing over were derived from a model proposed by Robin Holliday in 1964. Holliday's model was one of the first that explained most of the genetic data available at the time by a mechanism m involving the breakage, reunion, and repair of DNA molecules. Homologous recombination is an essential cellular process catalyzed by enzymes specifically made and regulated for this purpose.



**Function of Recombination**

1. Providing genetic variation,
2. Retrieve sequences lost through DNA damage by replacing the damaged section with an undamaged DNA strand from a homologous chromosome.
3. Recombination also provides a mechanism to restart stalled or damaged replication forks ("replication restart").
4. Special types of recombinations regulate the expression of some genes.

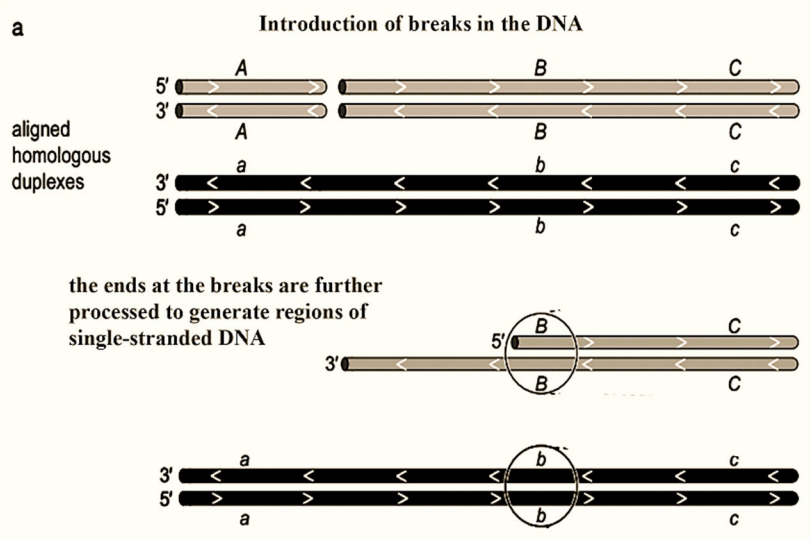
**Key steps of homologous recombination present in these models include the following:**

**1. Alignment of two homologous DNA molecules**.

By "homologous" we mean that the DNA sequences are identical or nearly identical for a region of at least 100 bp or so. Despite this high degree of similarity, DNA molecules can have small regions of sequence difference and may, for example, carry different sequence variants, known as alleles, of the same gene.

**2. Introduction of breaks in the DNA**

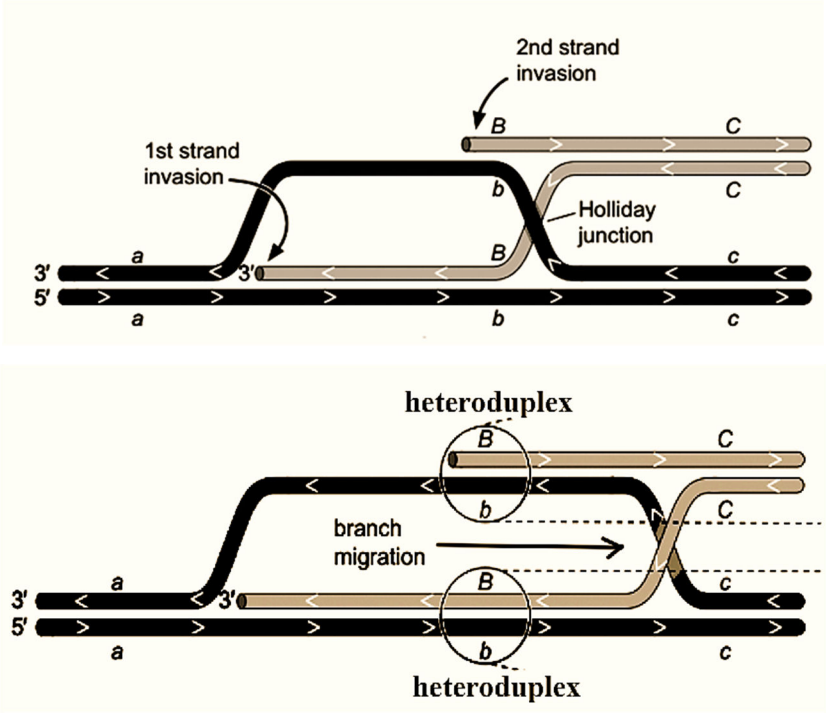
Once the breaks are formed, the ends at the breaks are further processed to generate regions of single-stranded DNA.




After introduction of the DSB, a DNA-cleaving enzyme sequentially degrades the broken DNA molecule to generate regions of single-stranded DNA (ssDNA). This processing creates single-strand extensions, known as ssDNA tails, on the broken DNA molecules; these ssDNA tails terminate with 3’ ends. In some cases, both strands at a DSB are processed, whereas in other cases, only the 5’ -terminating strand is degraded. Elongation from these DNA ends—using the complementary strand in the homologous duplex as a template—serves to regenerate the regions of DNA that were destroyed during the processing of the strands at the break site.

**3**. **Strand invasion**

The ssDNA tails generated by this process then invade the unbroken homologous DNA duplex. Initial short regions of base pairing are formed between the two recombining DNA molecules. This event is called strand invasion. As a result of the strand invasion process, regions of new duplex DNA are generated; this DNA, which often contains some mismatched base pairs, is called heteroduplex DNA.

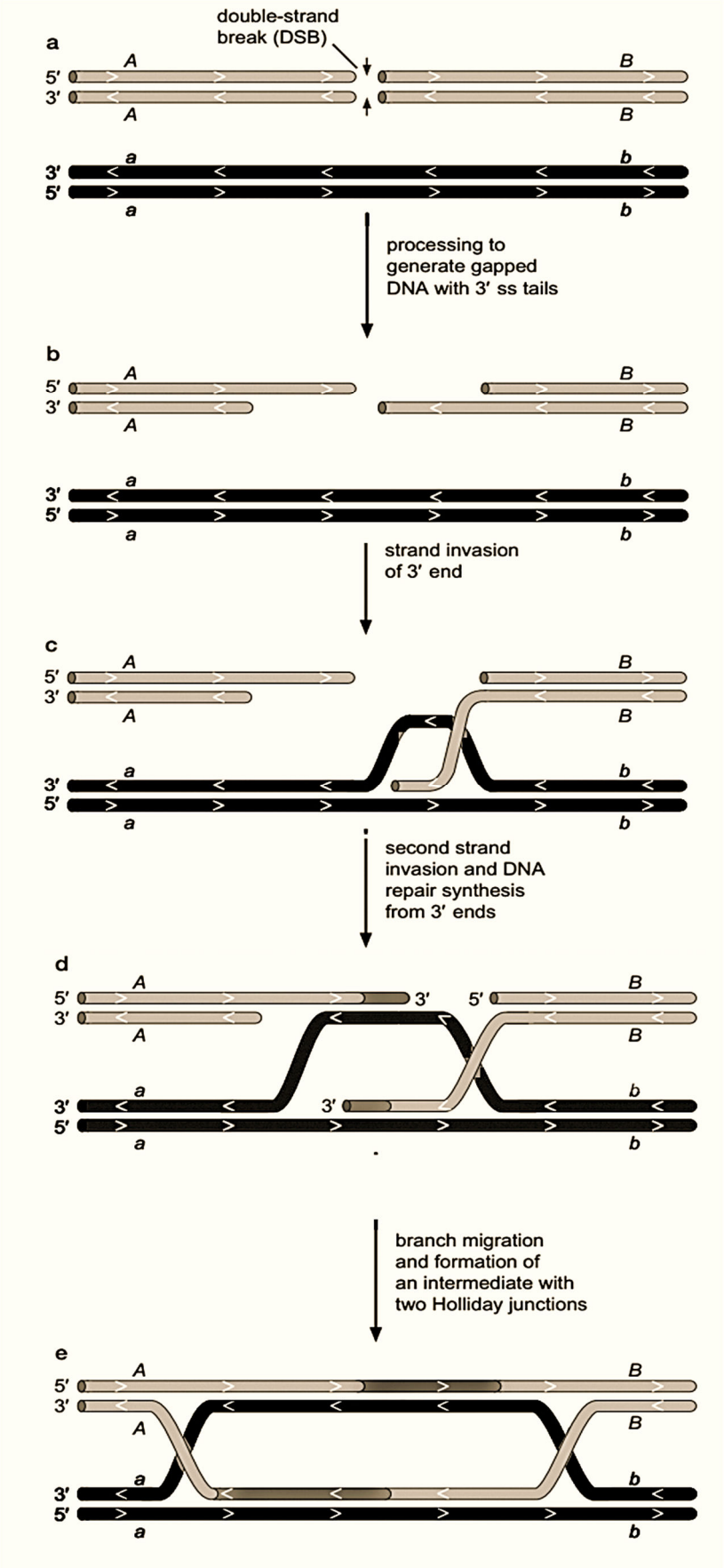



**4. Formation of the Holliday junction**

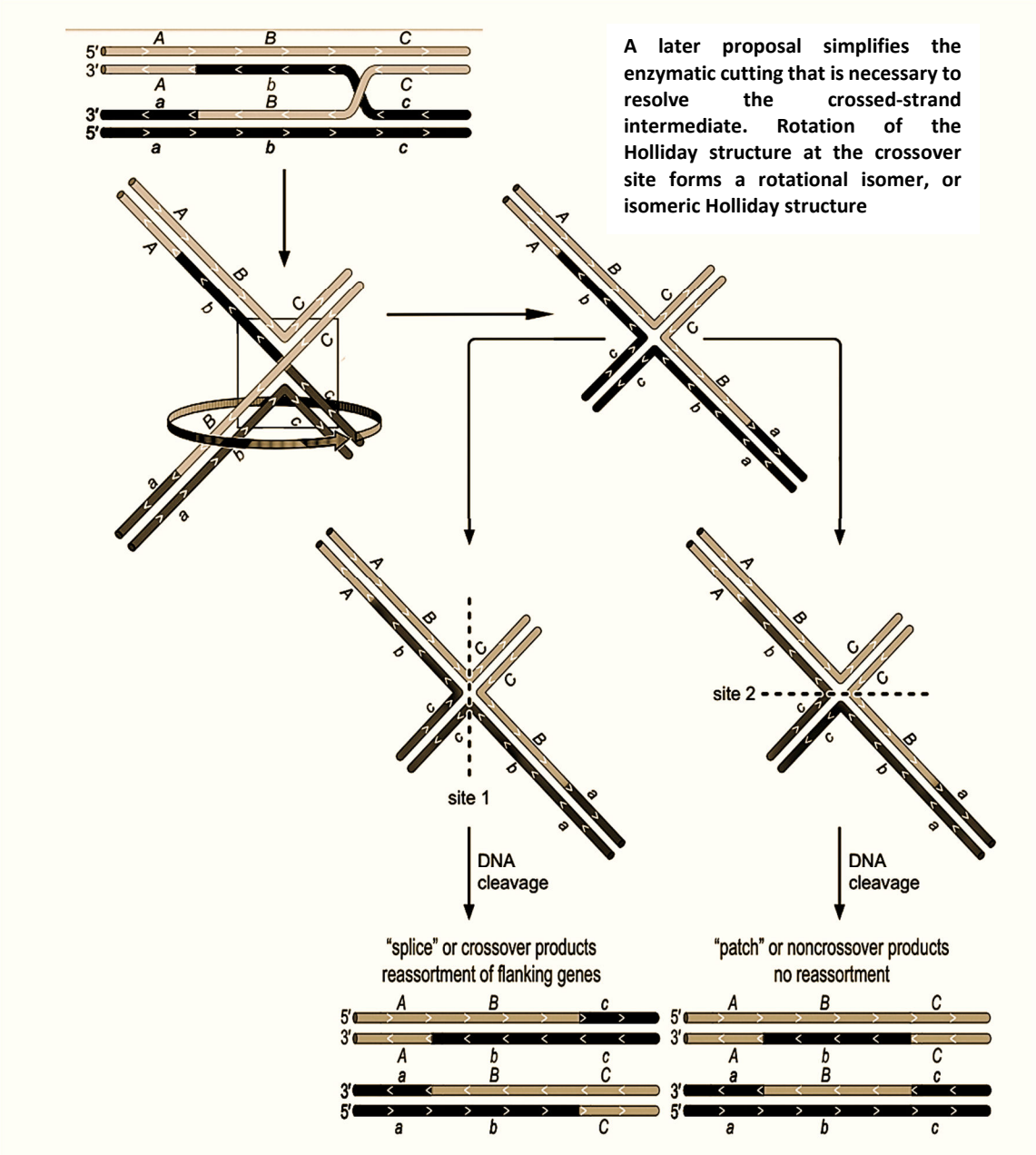
After strand invasion, the two DNA molecules become connected by crossing DNA strands to form a structure that is called a Holliday junction. This junction can move along the DNA by the repeated melting and formation of base pairs. Each time the junction moves, base pairs are broken in the parental DNA molecules while identical base pairs are formed in the recombination intermediate. This process is called branch migration.

**5.Resolution of the Holliday junction**

The process to regenerate DNA molecules and therefore finish genetic exchange is called resolution. Resolution can be achieved in one of two ways, either by cleavage of the Holliday junction or (in eukaryotes) by a process of "dissolution." In the first, cutting the DNA strands within the Holliday junction regenerates two separate duplexes. As we shall see, which of the two pairs of DNA strands in the Holliday junction is cut during resolution has a large impact on the extent of DNA exchange that occurs between the two recombining molecules.




**DSB-repair model for homologous recombination. Shown are the steps leading to generation of a recombination intermediate with two Holliday junctions.**




The two connected duplexes of this structure can be resolved (i.e., disconnected) by cutting and rejoining of only two strands. If this involves the two strands that were not cut to generate the original Holliday intermediate, the resulting "spliced" products are recombinant duplex chromosomes containing a heteroduplex region. However, if resolution involves cutting of the two strands that were originally cut, the resulting "patched" products are duplex chromosomes that contain a heteroduplex B region but are not termed recombinants, since all the markers to the left of A and to the right of C are derived from the same original chromosome.