MOLECULAR MEIOSIS* DRAFT

"Genes are in a sense immortal. They pass through the generations, reshuffling themselves each time they pass from parent to offspring… " *Richard Dawkins, The Selfish Gene*

Meiosis is the "reduction division" process whereby our genes are shuffled between maternal and paternal chromosomes and reduced from a diploid to a haploid state. In this activity, you will have the opportunity to model the molecular mechanism of this shuffling process known as "crossing over".

Note to teachers: Why would you want to teach molecular meiosis? Two reasons:

1. **Because it is hard**. When we simply say to our students *"genetic information is swapped between paternal and maternal chromosomes during meiosis in a process called crossing-over"* – we reduce this amazingly complex molecular process to an almost trivial piece of information. On the other hand, the molecular mechanism of crossing-over is complicated, and therefore it is understandable that we have not tried to teach it. With this molecular meiosis activity, we believe it is now possible to teach this hard topic to high school students.
2. Because this will **afford you the opportunity to spiral back** to some basic aspects of DNA biology that you have previously taught your students and allow them to apply their prior knowledge to this complicated molecular process. In particular, the previous knowledge your students will apply to this process includes:

    i. A DNA strand has a polarity, i.e. a 5' end and a 3'end.

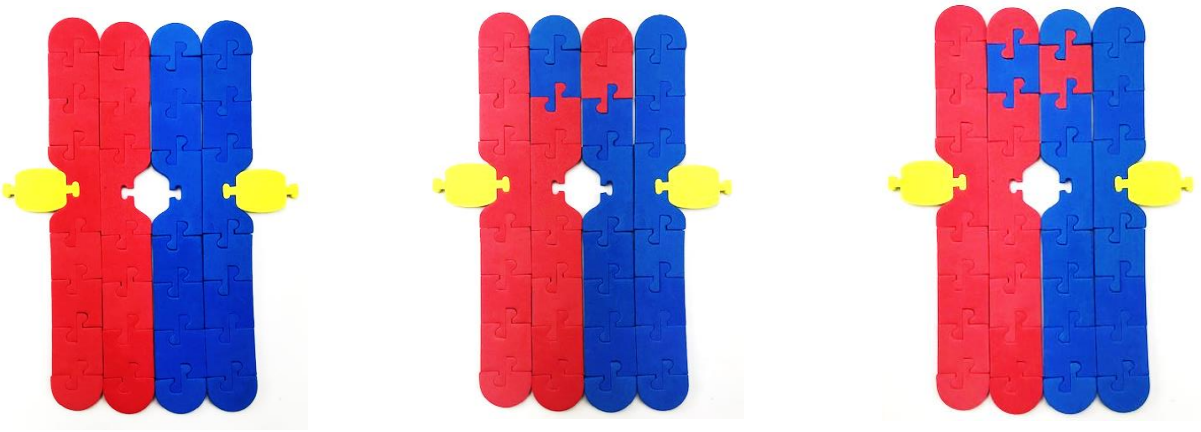
    ii. The two strands of DNA are antiparallel with AT and GC base pairs.

    iii. DNA polymerase synthesizes DNA in the 5' to 3' direction.

The crossing-over process that we want to model is an example of a more general process known as "**homologous recombination**". Homologous recombination was initially understood as a series of events that led to the repair of double-stranded breaks in DNA. We now recognize that a specific variation of this process allows for the deliberate exchange of genetic information between maternal and paternal chromosomes during meiosis.

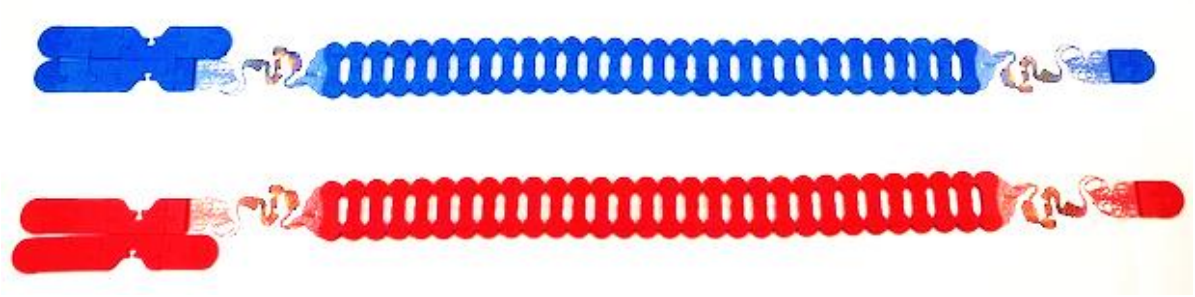
*This activity is based on the information in **Molecular Biology of the Cell**, 6th edition by Alberts et.al. – Figure 5-54 and accompanying text.

It is possible to teach a simplified version of "crossing over during meiosis" using the foam chromosome models without the added nucleotides. In this simplified approach, you can start with the two non-sister chromatids, one from Dad (blue) and one from Mom (red) (left). A single crossing over event – as modeled in the activity that follows – results in the swapping of **one end** of the blue paternal chromatid with the end of a red maternal chromatid (middle). Two crossing over events results in a paternal chromatid with a swapped **section** of the maternal chromatid and vise versa (left).

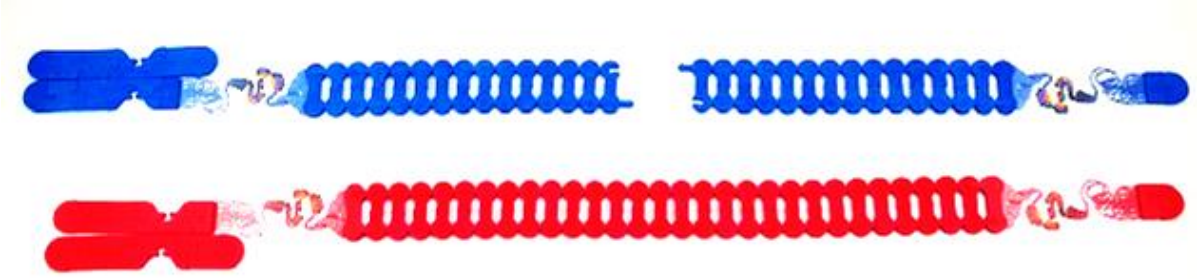


But crossing over is not simple. It is amazingly complicated. And now there are tools you can use to expose your students to the amazing complexities of crossing over. We will begin with foam models of two non-sister chromatids with a specific sequence of nucleotides inserted in the model.

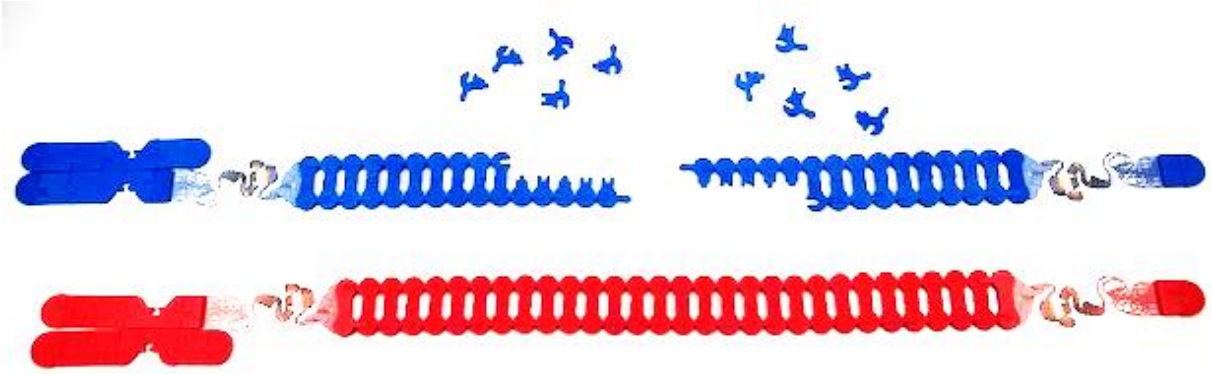
1. Imagine that the model shown below represents paternal (blue) and maternal (red) copies of human chromosome 11.



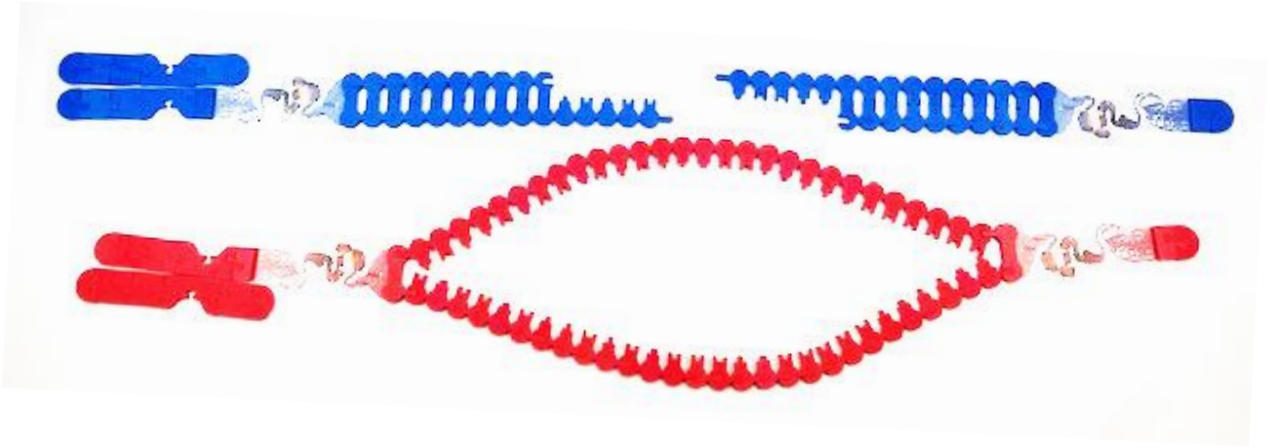
2. The homologous recombination that results in crossing-over during meiosis **begins with a bold step** – a double-stranded cut is introduced into one of the non-sister chromatids... the paternal copy in this example.



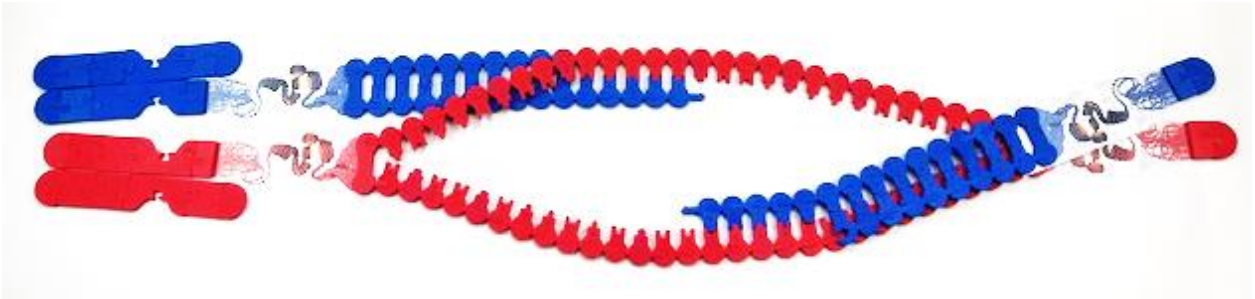
3. Following the double-stranded cut, a 5’ to 3’ exonuclease digests away one strand of DNA from each cut end…one nucleotide at a time, moving in the 5’to 3’ direction. The result of this exonuclease action is a short stretch of single-stranded DNA representing 3’ extensions on the cut paternal chromosome.



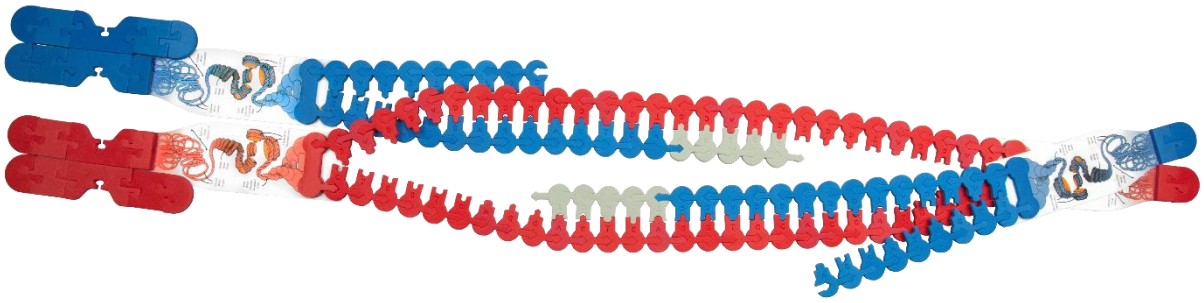
4. At the same time, the homologous DNA sequence on the maternal chromosome is denatured…in preparation for strand invasion.



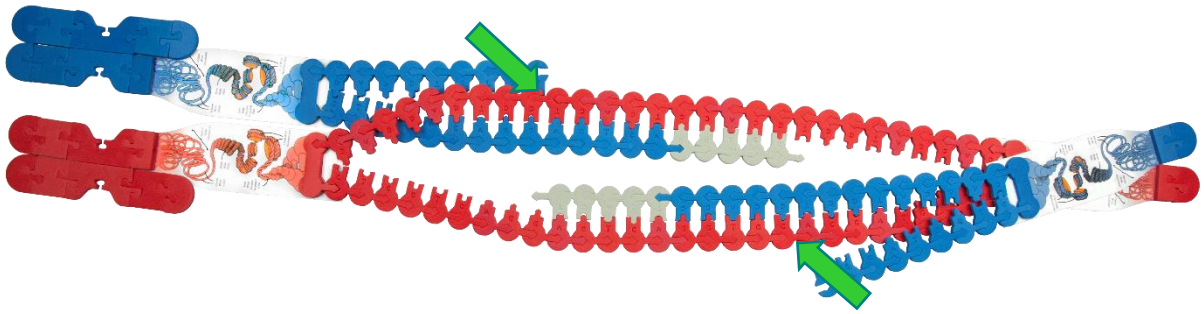
5. During strand invasion, the protruding 3’ ends of the paternal DNA form Watson/Crick base pairs with their homologous sequences on the material chromosome.



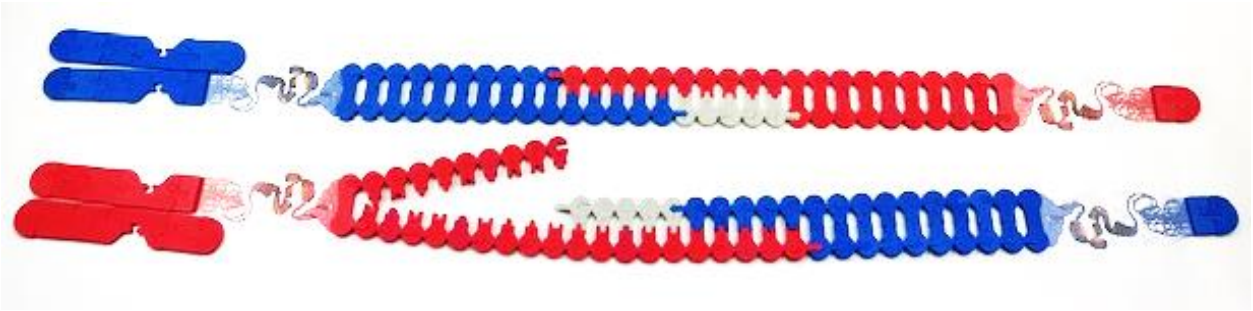
6. DNA polymerase then extends the 3’-OH primer of the paternal chromosomes synthesizing new DNA (grey nucleotides in this model) in the 5’ to 3’ direction.



7. To resolve these intertwined chromosomes, single-stranded cuts are introduced into the maternal DNA at the sites of the green arrows.



8. Ligation reactions then form the final phosphodiester bonds that seal up the single-stranded nicks in the chromosomes generating the chromosomes shown below.



Because multiple crossing over events occur along two homologous non-sister chromatids during meiosis, the red paternal chromosome will have patches of blue maternal chromosomes along its length, and vise versa.

All models are wrong, and one thing that is wrong with the above model of crossing over is that it does not include any of the many proteins that are required to make this happen, like (i) **Spo11** that cuts the DNA to initiate the process, (ii) the **5' to 3' exonuclease** that nibbles away the ends to create the 3' single-stranded extensions, (iii) **Brca1** that loads **Rad52** onto the homologous DNA in preparation for strand invasion, and the large complex of proteins (eukaryotic homologs of E coli **RuvA** and **RuvB**) that provides the scaffolding that holds all the DNA together throughout the process.