

What epigenetics is:

What is epigenetics? Let us explain this term using some analogies.

Take a look at your body. You can easily distinguish your eyes from your skin, and your nose from your mouth. Similarly, plants are also made of different organs: roots, stems, leaves, flowers etc. The reason behind such large diversity in living organisms comes from the existence of different tissues – groups of similar cells with a specialized function. Without this specialization we would be just a mass of simple cells that cannot, for example, walk or talk. Consequently, a plant would not be able to produce flowers or absorb sunlight. Even though the difference between cell types in your body is pretty evident, almost all the cells contain the same DNA. The DNA code is identical but is interpreted differently by different cell types. Epigenetics can be described as the tool by which DNA can be interpreted in different ways without changing the DNA sequence.

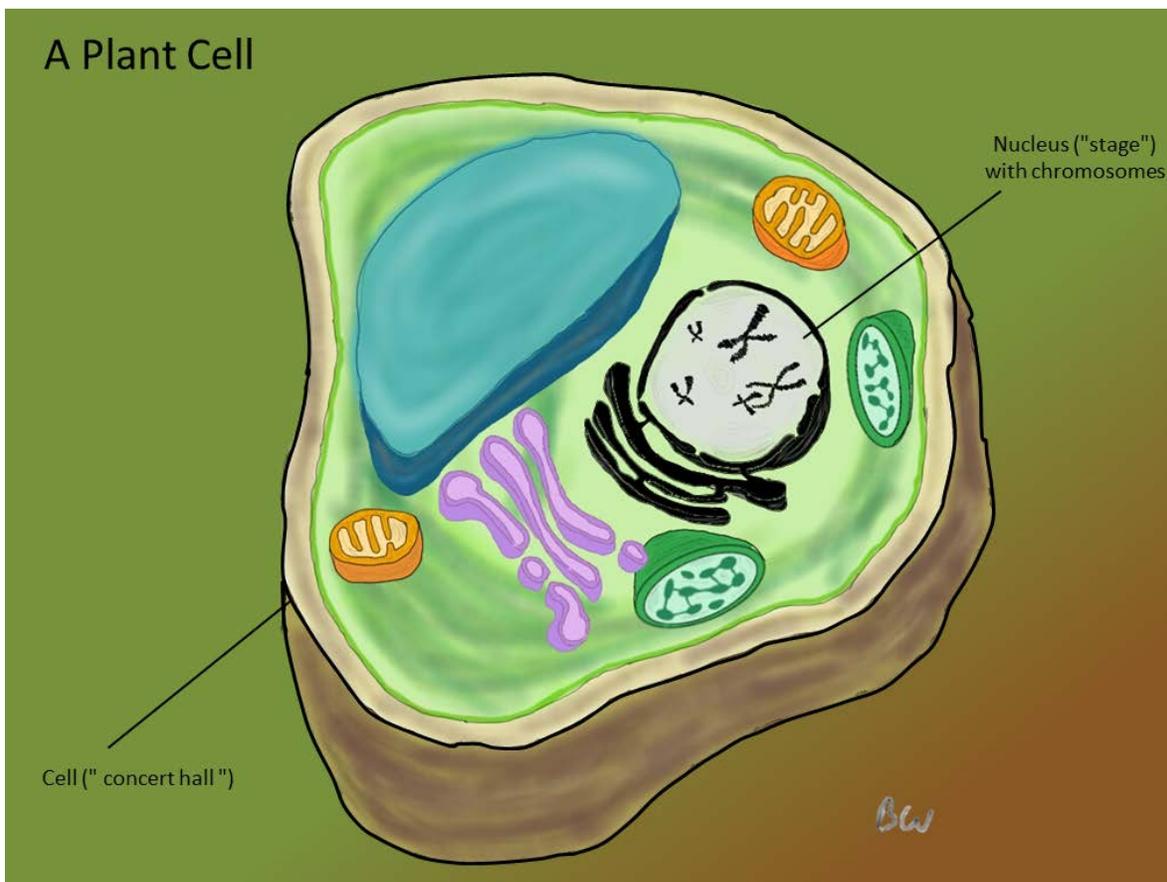


Figure 1 Cell and the nucleus in analogy to music.

We will explain epigenetics using an analogy to playing music. First, imagine each cell as a concert hall. At the center of it, stands the stage. This stage is the core of the cell: the nucleus. It is the place where chromosomes containing all the DNA sequences including genes are gathered. Genes

encode the genetic information that makes an organism: “the book of life”. The genetic code itself is based on the use of four letters A, T, G and C called nucleotides that assemble together to form the DNA double helix. Translation of one encoded sequence (one gene) leads to the formation of one factor (protein) and life itself relies on the simultaneous translation of many of these sequences (and therefore proteins). To transpose this in our musical allegory, DNA sequences (genes) are like music partitions where nucleotides are the musical notes. Translating the code of the different genes into proteins then resemble a situation where musicians come together to play different partitions and produce all the melodies that compose the symphony of life. To guide musicians on how and when to play a partition, music sheets are usually annotated with symbols that indicate the dynamics of the music, for example: “*ff*” for fortissimo (very loud) and “*pp*” for pianissimo (very soft). Importantly, these symbols do not change the notes themselves, just the way they are played. In similar manner, cells also contain “guidelines” on how a gene should be interpreted: Epigenetic marks. According to the given epigenetic indications, a gene can be (strongly) activated or silenced, depending on the cell you are looking at. Last but not least, a crucial aspect of epigenetic marks is their heritability. Marks will be transmitted through cell divisions or even from one generation to the other. This allows the establishment of a cellular memory. Interpretative annotations will be transmitted from the mother cell to both daughter cells therefore allowing maintenance of tissue identity. To explain this in music terms, it would be like parents giving a set of partitions to their children that encompass all the manuscript indications they have been adding to the partitions. Thus children would play partitions just like their parents used to do.

When compaction shapes gene expression:

Thus, everything revolves around the nucleus where all the genes are being stored and regulated. But this nucleus is a very small structure: The tenth of the width of a human hair. Given the number of DNA contained in the nucleus, compaction of DNA is required to fit in such small space. Nature indeed found a way to tackle this problem. A compaction is accomplished via wrapping of the DNA double helix around complexes of particular proteins (histones) therefore forming a structure called nucleosomes. To get a better picture, one could imagine a string (DNA) wrapped around beads (the histones). This process is in a way comparable to the use of compacted MP3s instead of a raw file that takes much more storage space.

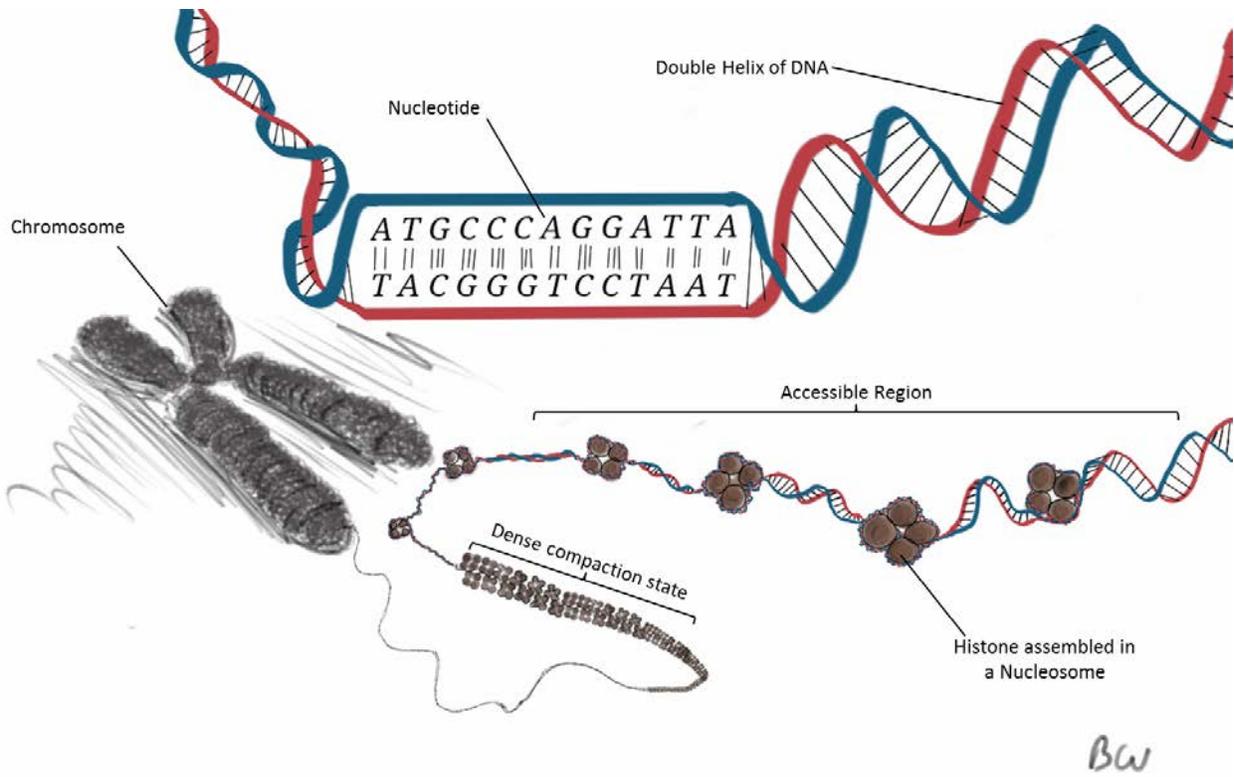


Figure 2 Compaction of DNA

Unfortunately, beauty often lies in complexity and the process of compaction is not that straightforward. High compaction of all the DNA sequences will almost certainly erase all the necessary information about a cell's behavior. No accessible partitions for the musicians, no music, no life. Therefore compaction needs to be applied in a selective way where dispensable genes would be compressed while crucial ones remain active. To annotate particular regions of DNA, the cell follows special instructions, called in biology: epigenetic modifications.

Epigenetic modifications:

We will distinguish the two major modifications associated with epigenetic gene regulation: DNA methylation and histone modifications. But before entering into a detailed description, it is important to remember that epigenetic factors and modifications do not change the DNA sequence. They leave the sequence of nucleotides as it is. Instead, they influence the interpretation of DNA – in a symphony, the way the partition will be played by the musicians e.g silent, pianissimo (*pp*) or loud, fortissimo (*ff*).

DNA methylation:

This layer of epigenetic regulation acts on the sequence of DNA, more precisely on the C letters of the genetic code. Remember, no modification is made to the original sequence. So the

DNA sequences stay the same. Only, DNA methylation adds a “red mark” called a Methyl group on top of the C. Overall, DNA methylation mostly impairs gene expression, this by reducing accessibility either directly or indirectly. The context of this mark is also an important aspect of it. In mammals, only C preceding G letters can be methylated. This point is actually crucial for the heritability. But in plants, our main interest among the EpiTRAITS consortium, the context of DNA methylation is broader with C preceding G letters, C preceding H and G or H and H letters (H being either a A, a T or a G) and brings extra interrogation on how heritability is established in the latter context.

Histone Modifications:

This second layer of epigenetic regulation acts on histones associated with DNA, the ‘beads’ on which DNA is wrapped around. Histones, similarly to the C letters in DNA, can be modified. Histone modifications are ruled by a specific code referred to as the “histone code”. According to the category of genes they are targeting, the modifications will not be the same. For instance, active genes are often associated with acetylation marks which act as “green positive flags” while methylation marks often act as “red negative flags”. “Activating” histone marks will ensure a relaxed state of compaction and shapes accessible DNA regions while “repressive” Histone marks will lead to a higher degree of compaction, meaning less accessibility and inactive genes.

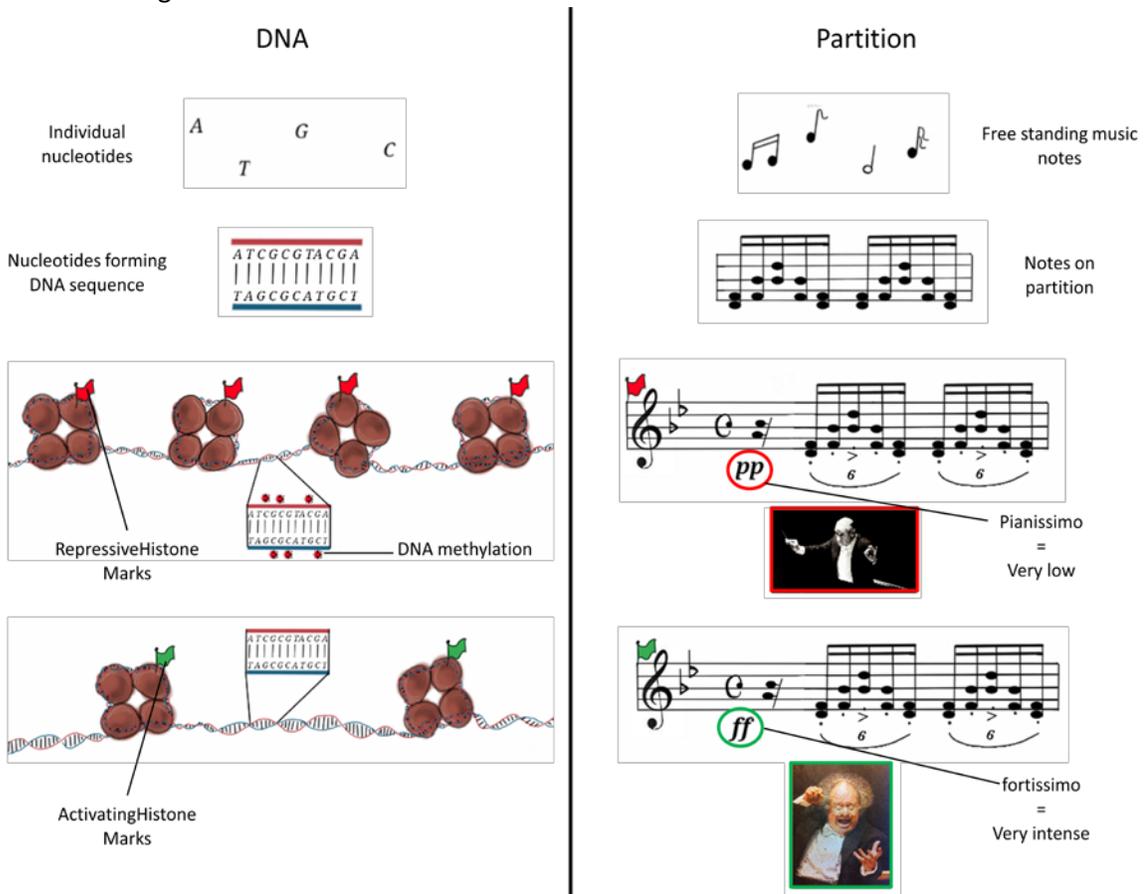


Figure 3 Dynamics of gene regulation as musical notation.

Conclusion:

Altogether, from one “book of life” containing the same partitions in every cells, epigenetics conducts a cell specific symphony. By selectively silencing or fine tuning the way each partitions has to be played, epigenetic regulation adapts the symphony depending on the cell type. If you could hear it, it would be like having one specific composition for leaf cells, another for root cells and another one for flower composing cells. As mentioned earlier, epigenetic defines guidelines that are heritably passed from one generation to the next. But beyond serving the purpose of establishing a cellular memory, this heritable aspect, combined with the dynamic aspect of epigenetic modifications is deeply questioning our vision of classic evolution. Interestingly, epigenetic marks have been found to be under the influence of both internal and environmental signals which ultimately influence gene expression. For instance, an organism such as plant, when exposed to a specific stress (drought, cold, warm, pathogens etc.) can acquire a higher stress resistance via epigenetic mechanisms and possibly transmit this better fitness to its progeny. Thus, epigenetic inheritance tends to blur the boundary between nature and nurture, what comes from the fixed DNA code and what you gain from the environment, by editing an extra code on top of the first one. The final word should be given to Sir Conrad Waddington, who firstly coined the modern term of epigenetics and declared that an epigenetic consideration of the theory of evolution would go some way toward healing it.

See more:

For more information about epigenetics:

<http://www.epigenesys.eu/en/homepage>

<http://learn.genetics.utah.edu/content/epigenetics/>

<http://www.nature.com/scitable/spotlight/epigenetics-26097411>

Blaise Weber, Pawel Mikulski

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