

# A Classical Model of DNA Stability

Podcast Learn & Fun \*

January 18, 2025

Hydrogen bonds are non-covalent interactions crucial for the structure and stability of many biological molecules, including DNA. In the case of DNA, these bonds form between complementary nitrogenous bases on opposite strands of the double helix. For instance, adenine pairs with thymine through two hydrogen bonds, while guanine pairs with cytosine through three hydrogen bonds. These interactions play a vital role in maintaining the helical structure of DNA and ensuring that the genetic information it encodes remains stable.

To mathematically model the interactions between the base pairs in DNA (adenine-thymine (A-T) and guanine-cytosine (G-C)) and their impact on the helical structure of DNA, we can employ a combination of physics, chemistry, and molecular biology principles. Here, we focus on the hydrogen bonding interactions and their influence on the stability of the DNA double helix.

## Hydrogen Bonding Interaction Model

We model the hydrogen bond interactions between the base pairs as an energy minimization problem, where the system seeks to find the configuration that minimizes the total free energy,  $E_{\text{total}}$ , associated with the hydrogen bonding.

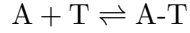
When base pairs form through hydrogen bonds, they follow the principles of chemical equilibrium. The hydrogen bonds between the complementary bases in the DNA molecule form and dissociate based on the relative concentrations of the base pairs. The equilibrium constant  $K$  for this process can be expressed thermodynamically.

Consider the equilibrium reaction for base pairing between adenine (A)

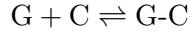
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and thymine (T) or guanine (G) and cytosine (C): For the A-T pair:



For the G-C pair:



The equilibrium constant  $K$  for each base pairing reaction is related to the Gibbs free energy change ( $\Delta G$ ) of the reaction at a given temperature  $T$ . For the reaction  $A + T \rightleftharpoons A-T$ , the Gibbs free energy change  $\Delta G_{A-T}$  is:

$$\Delta G_{A-T} = -k_b T \ln(K_{A-T})$$

Similarly, for the reaction  $G + C \rightleftharpoons G-C$ , the Gibbs free energy change  $\Delta G_{G-C}$  is:

$$\Delta G_{G-C} = -k_b T \ln(K_{G-C})$$

where  $k_b$  is the Boltzmann constant,  $T$  is the absolute temperature in kelvins, and  $K_{A-T}$  and  $K_{G-C}$  are the equilibrium constants for the A-T and G-C base pairing reactions. The negative sign in these expressions indicates that as the equilibrium constant  $K$  increases (more base pairs formed), the system releases energy and stabilizes.

The equilibrium constant  $K$  is related to the number of hydrogen bonds between the bases. Specifically: For an A-T pair, there are 2 hydrogen bonds formed, and the equilibrium constant  $K_{A-T}$  reflects the contribution of these two bonds to the overall stability of the base pair. For a G-C pair, there are 3 hydrogen bonds formed, and  $K_{G-C}$  reflects the contribution of these three bonds.

In a general sense, the equilibrium constant  $K$  can be related to the number of hydrogen bonds,  $N$ , by the following general expression:

$$K \propto e^{-\Delta G/k_b T}$$

Since the number of hydrogen bonds influences the Gibbs free energy change  $\Delta G$ , which in turn affects the equilibrium constant  $K$ , we expect that for the G-C pair (with 3 hydrogen bonds), the equilibrium constant will be higher than for the A-T pair (with 2 hydrogen bonds), due to the additional hydrogen bond contributing to a lower free energy and greater stability.

Thus, the energy  $E_{\text{pair}}$  associated with the formation of each base pair can be written as:

$$E_{A-T} = -k_b T \ln(K_{A-T})$$

$$E_{G-C} = -k_b T \ln(K_{G-C})$$

These equations express the energy required to form an A-T or G-C pair in terms of the equilibrium constants  $K_{\text{A-T}}$  and  $K_{\text{G-C}}$ , which depend on the number of hydrogen bonds.

For a DNA strand composed of  $n_{\text{AT}}$  A-T base pairs and  $n_{\text{GC}}$  G-C base pairs, the total energy  $E_{\text{DNA}}$  is:

$$E_{\text{DNA}} = n_{\text{AT}}E_{\text{A-T}} + n_{\text{GC}}E_{\text{G-C}}$$

## The Twist and Supercoiling of the Helical Structure

The DNA molecule adopts a helical structure, twisting around an axis. This helical twist plays an essential role in maintaining the stability and functionality of the molecule. The term “twist” refers to the number of base pairs per complete  $360^\circ$  turn of the helix.

In a B-form DNA helix, the typical twist is approximately 10.5 base pairs per turn. This means that for every 10.5 base pairs along the length of the helix, the molecule makes a full  $360^\circ$  rotation around its axis. This is referred to as the twist per base pair  $\tau_{\text{bp}}$ .

When a DNA molecule is twisted, it experiences *torsional strain* due to the forces that resist twisting. Torsional strain is a form of mechanical strain that results from the deformation of a molecule due to a change in its twist. It is important for maintaining the stability of the DNA double helix and for processes like DNA replication and transcription, which involve unwinding and overwinding of the DNA.

To model the DNA’s helical twist, we first need to consider the twist in terms of the number of base pairs per turn. If we assume that the DNA helix has  $n_{\text{bp}}$  base pairs and a characteristic twist per base pair of  $\tau_{\text{bp}}$ , the total twist is given by:

$$\tau = \frac{n_{\text{bp}}}{\tau_{\text{bp}}}$$

where  $\tau$  is the total torsion (or total twist) of the DNA helix,  $n_{\text{bp}}$  is the total number of base pairs in the DNA strand, and  $\tau_{\text{bp}}$  is the number of base pairs per complete  $360^\circ$  turn of the helix (typically 10.5 for B-form DNA).

The total torsion  $\tau$  can induce an energy cost in the system. When the DNA helix is either overtwisted or undertwisted (compared to the natural 10.5 base pairs per turn), the molecule experiences strain due to the extra or missing twist. This strain can be quantified using a formula for the energy of torsional deformation. We define the deviation from the natural twist as:

$$\Delta\tau = \frac{n_{\text{bp}}}{\tau_{\text{bp}}} - \tau_0$$

where  $n_{\text{bp}}/\tau_{\text{bp}}$  is the actual number of turns in the helix, and  $\tau_0$  is the natural twist (typically 10.5 base pairs per turn). This deviation  $\Delta\tau$  represents the torsional strain in the system.

The energy  $E_{\text{torsion}}$  associated with torsional strain can be modeled as a quadratic function of the deviation from the natural twist (similar to the potential energy stored in a spring):

$$E_{\text{torsion}} = \frac{1}{2}C_{\text{twist}}(\Delta\tau)^2$$

where  $C_{\text{twist}}$  is a constant related to the stiffness of the DNA helix and represents the resistance to twisting (i.e., the rigidity of the helical structure). Substituting the expression for  $\Delta\tau$  into the energy formula, we obtain:

$$E_{\text{torsion}} = \frac{1}{2}C_{\text{twist}}\left(\frac{n_{\text{bp}}}{\tau_{\text{bp}}} - \tau_0\right)^2$$

This expression represents the energy cost due to torsional strain when the DNA helix is twisted beyond its natural configuration (either overtwisted or undertwisted).

## Overall DNA Stability

The overall stability of a DNA molecule can be described by its total free energy, which combines the energetic contributions from both the base pairing and the helical structure. The total free energy  $E_{\text{total}}$  is:

$$E_{\text{total}} = E_{\text{DNA}} + E_{\text{torsion}}$$

Substituting the expressions for  $E_{\text{DNA}}$  and  $E_{\text{torsion}}$ :

$$E_{\text{total}} = (n_{\text{AT}}E_{\text{A-T}} + n_{\text{GC}}E_{\text{G-C}}) + \frac{1}{2}C_{\text{twist}}\left(\frac{n_{\text{bp}}}{\tau_{\text{bp}}} - \tau_0\right)^2$$

This expression allows us to evaluate the total stability of the DNA structure by considering both the specific hydrogen bonding between base pairs and the torsional strain due to the helical twist.

The stability of the DNA structure can be further modulated by environmental factors, such as temperature and ionic strength. The effect of temperature is already included in the expression for the base pair energies via the Boltzmann factor. Additionally, ionic strength affects the electrostatic interactions between the negatively charged backbone and can influence the

stability of the double helix, which can be incorporated into the equilibrium constants  $K_{A-T}$  and  $K_{G-C}$ . The higher number of hydrogen bonds in G-C pairs compared to A-T pairs means that DNA with more G-C content will be more thermally stable (higher melting temperature).

The helical twist ensures that the DNA molecule stays in a compact, organized structure. However, if the DNA is twisted too much (positive supercoiling) or not enough (negative supercoiling), this introduces torsional strain. The base pair interactions (through the hydrogen bonds between complementary nucleotides) help to stabilize the structure by holding the strands together. This balance between torsional strain and base pairing ensures that the DNA maintains its structural integrity even under mechanical stress (such as during processes like transcription and replication).