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DNA Transcription Regulation by Biochemistry and Physics: A Review

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Abstract

As Science advances with the development of greater improvements in each discipline, we are able to begin to unravel more of the mechanisms involved in DNA transcription with a multi-disciplinary approach. The Biochemistry influences the structural changes leading to changes in the physics and energy of the cell during transcription. Non Histone Proteins (NHP) from the cytoplasm are directed into the nucleus to phosphorylate, acetylate and methylate specific sections on corresponding Histones for a tertiary structural change. The DNA, which is wound around the Histones in a bifilar type winding, can then be modified in its structure to supercoiling, thereby allowing the formation of special toroidal structures of DNA strands. These supercoiling structures have been shown to increase energy concentration. One of the most important coils seen in DNA transcription is the torus, or Moebius coil. It is formed by the structural changes in the DNA from the Histone enzymatic modifications by the NHPs and by the polyamine, spermidine. This structural change is seen more dramatically as the coil is pulled apart in the DNA strands. The DNA becomes more organized into these coils and the electro-magnetic properties of the DNA in this new Moebius coil, or torus, produces vortices which are thought to be responsible for the incorporation of specific enhanced magnetic fields or, thought by some, to be involved longitudinal wave conduction. These fields are observed to transmit energy and possibly information, which may play an even larger role in the transcription process. The Quantum fields mentioned in earlier studies in biological systems may very well be employed by the structural change in the DNA to allow these fields to transfer energy and information for the transcription process. Transcription requires this specificity of energy to transcribe but it is not yet known if the energies work with ATP or actually increase ATP needed for transcription.

Keywords DNA transcription; Quantum fields; Histone proteins; RNA polymerase; Supercoiling

Transcription

Transcription is the process by which information in a strand of DNA is copied into a new molecule of messenger RNA (mRNA). DNA stores genetic material in the nuclei of cells as a template. mRNA carries this information transcribed from the DNA, out of the nucleus. mRNA, which carries the same information from the DNA, is not an identical copy of the segment. Instead, its sequence is predominantly complementary to the DNA template. RNA polymerase carries out the transcription process along with several accessory proteins called transcription factors. Transcription factors can bind to specific DNA sequences called enhancer and promoter sequences to recruit RNA polymerase to an appropriate transcription site. Together, the transcription factors and RNA polymerase form a complex called the transcription initiation complex [1].

In the synthesis of the nucleic acid RNA, ATP is one of the four nucleotides incorporated directly into RNA molecules by RNA polymerases and that the energy driving this polymerization has been thought to come from the cleaving off of a pyrophosphate (a diphosphate oxyanion). However, this Biochemical energy source does not appear to be the only source of energy for DNA transcription [2]. The complex initiates transcription, but only after structural changes occur in the DNA following structural changes in the histones and changes in the supercoiling of the DNA [3,4].

There are four major core histone bodies in the DNA; H3, H4, H2a and H2b [5]. Each area correlates to a certain part of the DNA. The DNA is wound around each histone core to form a nucleosome. Each nucleosome core particle has a complex of 8 histone proteins [6-8]. When a NHP enters the nucleus, it changes the structure of the specific histone it is directed to by enzymatic alterations [5,9,10]. NHPs regulate transcription by altering the structure of histones [11]. Deacetylation is only one of the enzymatic changes affecting the structure of the histones and transcription of DNA. These structural effects on the histone then allow tertiary changes that pull DNA apart from a double strand to a single strand and expose specific sections of DNA as well as creating a new coil structure within the single DNA strand. This coil structure during transcription has been shown to be the Moebius coil and is said to be an effective form for a super conductor for electromagnetic fields [12].

These structural changes in the histones are a direct result of the acetylation, phosphorylation and/or methylation of the histones around which the DNA is wound in a double strand helical form [5,13]. The histone structure is changed by the NHPs coming from the cytoplasm [14]. The NHPs then change the DNA structure and pull it away from being a double strand to a single strand, changing the basic helical form by making loop-like structures [4,15]. Thereby NHPs determine transcription of DNA into RNA [16]. The DNA becomes more organized into supercoiling, torus, and Moebius coils. These structural changes increase the electrical and magnetic properties of the DNA, and form vortices, which are proposed to enhance incorporation of energy [17].

The incorporation of electro-magnetic fields is also thought to play a general role in DNA activity [18]. Longitudinal waves can exhibit a so called "over-unity effect", meaning they are able to collect electromagnetic energy from the surrounding and send it to the receiver with a higher energy than the input [19]. Were longitudinal waves to be confirmed in DNA transcription, it would possibly provide a base for further extensive research of Quantum Fields in biological systems. It appears that there is an amplification of energies required for transcription, potentially utilizing multiple disciplines in its process.

Quantum Fields in Biological systems

DNA is constantly oscillating carrying waves along its path through trajectory bubbles as well as at the transcription gates [20-22]. Two primary mechanisms of charge transport have been examined in detail in previous research on DNA [23,24]. Over short distances, an electron displays the properties of a wave, permitting it to pass straight through a DNA molecule. It was proposed that a solitary wave could play a fundamental role in the process of transcription [23]. The process in a quantum mechanical effect known as tunneling has also been reported [24]. Stretching of DNA decreases the activity. However the supercoiling would increase the conductance and supercoiling is shown in early stages to activate DNA transcription [25]. These waves begin on conformational excitation points (called solitons) in DNA, and travel to make structural changes further along on DNA. They open up the DNA bases and close them again as new sections open up along the DNA in waves of activity [26].

Atoms repulse each other when brought close together. In supercoiling, this appears to be the case. It is related to the Pauli principle: when the electron clouds surrounding the atom start to overlap, the energy of the system increases abruptly or even exponentially [27]. Thus, the supercoiling and condensing of atoms could explain the extra energy involved in transcription as potentially coming from this source.

The proposal of a quantum level of bioenergy fields, rather than electrical magnetic fields (EM), was proposed by Cope in the mid-1970s [28]. He obtained preliminary evidence that certain biomolecules could act as super conductors. It was demonstrated that the EM fields in the body are quantized, showing that biological systems are a single magnetic flux quantum [29]. Biological systems are said to be capable of functioning at the quantum level as well as the classical level recognized for most biochemistry. Since the body is a quantum system according to Smith, it will not only respond to potential fields in the absence of classical EM force fields, but the action of potential fields may occur through quantum fields [30]. Potential fields are associated with magnetic vector potentials and electrostatic scalar potentials. EM fields are more fundamental. However quantum fields are considered a discovery of another type of energy, similar to Bohm's information and those described in quantum field theory [31]. Potential Fields may be considered as a bridge between the "higher order" Quantum fields and the more familiar classical EM fields.

Parallel coils (bifilar) can be either flowing in the same direction or in opposing directions, which are the self-canceling coils such as was originally proposed and developed by Tesla. Bifilar, toroidal and Moebius coils will generate force fields, potential fields and quantum fields in varying ratios depending on their structural change and the direction of their respective vortices. Tesla demonstrated that these coils could transmit energy over long distances without losses [32,33]. These waves were described in many ways such as longitudinal waves (where classic fields are transverse), scalar waves (where classical fields are vectors), force-free fields (where classical fields have force), time reversed waves (where classical fields travel forward in time), solitary waves and tachyon energy. Quantum fields are not electro-magnetic in nature as are fields from force fields and potential fields.

Experiments on cell division show a dramatic increase in cell transcription suggested from terahertz radiation [34]. The question arises; how does the energy change with the structure and how much involvement is derived from physics and quantum physics after these structural changes occur from the biochemical interactions in vivo of a biological system?

Replication and Transcription

DNA that is stable is in a right-handed helical form. In studies of replication and transcription in the laboratory using DNA and polymerase from cells it was shown that these processes of transcription couldn't go on unless the DNA is twisted into left-handed super helical turns. This uncoiling promotes unzipping of the double helix at certain points. It appears the histone involvement here, with its tertiary structural changes, may be responsible for these specific points exposures and the twisting to the left handed super helical form of double helix. Additionally, this twisting is creating a Moebius coil. When double stranded DNA is not transcribing it is wrapped around the histone body in a helical structure, however before transcription it becomes supercoiled, showing a Moebius structure and a single strand of DNA which is then pulled out as a loop for transcription [12]. This structural change may be to incorporate the additional energy required in this process. The supercoiled single stranded helix form for DNA is left handed for transcription, whilst the double stranded non-transcribing DNA is right handed. Super coiled DNA binds polymerase more readily and directs DNA synthesis much faster. The tightness of the super helix determines the rate of transcription [35].

The exactness of the transcription depends on which histones are modulated by Non Histone Proteins (NHP) by acetylation, methylation or phosphorylation. Each location and effect allows for a different section of the double helix to separate into a transcription ready left-handed helix of specific coding capabilities. Spermidine can modify the right-handed DNA helix containing a CGGC base pair to a left-handed helix, as can methyl groups on the cytosine bases in DNA [36]. Spermidine is elevated in all cell replication, including tumor promotion. It is a product from the enzyme ornithine decarboxylase (ODC), the rate-limiting enzyme in DNA synthesis [37]. In Cancer, ODC appears to be locked in its active form and does not reverse. In addition, methylation of DNA is seen with viral infections thought to be a form of defense against the virus but perhaps a form of cell survival encouraging transcription or replication. In cancer, methylation of histones is being found in certain types of tumors and may be involved in general cellular replication [38].

The Complexity of Transcription

There is a variety of computational-based approaches to analyze, modulate, and predict epigenetic modifications in given sequences. In the case of detecting DNA methylation, efforts have mainly devoted to discover of methylated CpG islands and allele specific cytosine methylation. The CG dinucleotides are mostly scarce throughout genome, especially in vertebrates [19] and mainly clustered in the

regions called CpG islands (CGIs). These rich regions with CG dinucleotides, CGIs, are interestingly located at the promoter of coding and non-coding genes, making them very attractive for researchers [19,20]. Because altering DNA methylation patterns of CGIs play essential roles in controlling the gene expression and silencing in various biological processes, such as X-chromosome inactivation, imprinting, silencing of intragenomic parasites [21,22] and especially in the epigenetic causes of cancer [21]. Due to CGIs essential implications in mentioned processes, multiple algorithms (either specific species or general purpose) have been developed to identify CGIs in the genomes. In this context, Gardiner-Garden and Frommer were the first who used an algorithm to study CGIs and G+C content in the genome of vertebrates. Subsequently, many other methods based on different algorithms had been developed [23-25]. Of these methods, artificial neural networks (ANN) and support vector machines (SVM) have broadly been used to analyze DNA methylation. Marchevsky et al. trained ANN with molecular data in order to classify lung cancer cells based on DNA methylation marker. They provided evidence that ANN could be used as a powerful approach for detecting DNA methylation. Das et al. indicated that SVM could predict methylation status of CpG regions with accuracy of 86%. They used this method to depict methylation patterns of all 22 human autosome chromosomes. The methods such as hidden Markov models (HMM), logistic regression, K-nearest neighbors and decision trees have also been used for this purpose [26,27], for example Barazandeh et al. disclosed significant correlations between CGI density and genomic features such as chromosome size, GC content, ObsCpG/ExpCpG, gene density and recombination rate in cattle. However, these methods were suffering from several disadvantages. First, these methods lacked systematic selection methods for a length threshold [28]. Second, they were unable to detect weak CpG islands [29]. Third, they were sequence-based to identify CpG islands and failed to distinguish between genuine CpG islands and CpG-rich regions [30]. To overcome these drawbacks, Bock et al. suggested epigenome prediction method and used integrates DNA methylation, polymerase II preinitiation complex binding, histone H3K4 di- and trimethylation, histone H3K9/14 acetylation, DNase I hypersensitivity and SP1 binding as criteria to map CpG islands. Their method could distinguish between weak and stronger CpG islands and use feathers of genomic DNA sequences and epigenome [31].

In respect to modifications of CGIs, the methylation is not only modification. Studies on the mammalian genome have demonstrated that in addition to methylation, there are other forms of modification including hydroxymethylation, formylation, and carboxylation [32-34]. The specific roles of these type modifications are still little known, but it has been hypothesized that these types might be intermediate steps during methylation and demethylation processes or even they may have own implication in diseases [35,36]. Furthermore, the three high-resolution structure of chromatin revealed two methylations, two hydroxymethylations, and five formylations have effects on DNA dodecamers, while methylation and hydroxymethylation alone have not any effects on the geometry of DNA [37,38]. These imply this fact that for fully understanding of CGI modification effects on chromatins structure; consequently, altering expression of genes it is critical that analyzing methods must include all of the modification possibilities. One of the computational methods that meet these criteria is reported by Krawczyk et al. in which they extended Natural Move Monte Carlo to simulate the conformation changes of chromatin as consequence of epigenetic modifications [39].

In the case of prediction, modeling and analysis of histone modifications, some methods have reported, such as simplified stochastic model [40], genome-wide chromatin analysis [41], and genome-wide mapping [41]. From the machine-learning methods have been used to detect histone modifications (acetylation, methylation, phosphorylation) we can mention to HMM approach, using chromatin signatures, model based on the prediction of pH-dependent aqueous solubility, and HMM based on the domain-level behavior. Benveniste et al. recently showed that histone modification prediction could achieve from knowledge of transcription factor binding at both promoter and distal regulatory elements. Furthermore, the methods such as QSAR analysis, homology modeling, and molecular docking methods have used for detecting histone modifications. These tools have well been used for deciphering epigenetic effects on various biological processes. Furthermore, using interaction between epigenetic, genetics and environment can improve estimation of breeding values and reduce their biases.

The histone code hypothesis articulates that the roles of histone post-translational modifications (PTM) are well descripted when the combinations and sequences of histone PTMs are accounted. Based on this hypothesis, several computational methods were developed for identification of histone modifications. ChromaSig and ChromHMM are two computational methods have been developed for this purpose. These methods are based on multivariate Hidden Markov Models and are able to show histone modifications and chromatin statues. Given that only subsets of the histone PTM combinations take place in nature, the later approaches were developed based on partial correlations and maximum entropy modeling. These methods have been used for identification of pairwise and high-order interactions between chromatin factors (Figure 1).

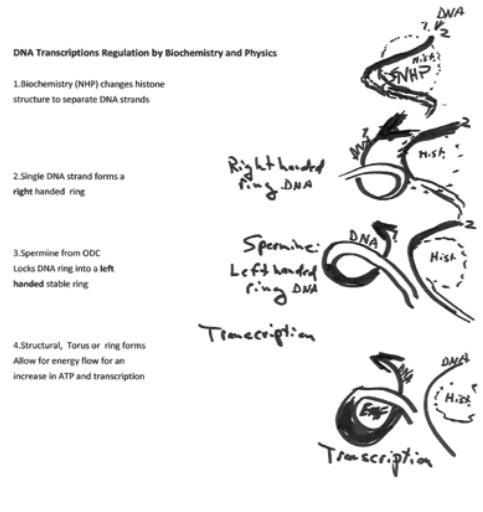

Figure 1: DNA transcription regulation by biochemistry and physics.

Summary

Past literature hinted at the mechanisms involved in DNA transcriptions, however our knowledge was not as advanced as it is now to understand the magnitude of the information presented. Our understanding of physics and biochemistry has greatly improved over the years, allowing us to further understand the amazing complexity of

DNA transcription and how it uses several areas of science to explain its complexity. Biochemistry is involved not only through van der Waal forces and hydrogen bonding but also through its ability to change structural forms. These then are capable of incorporating physics, or quantum physics, for the energy needed to allow an efficient, practical utilization of these energies and biochemical factors working together for transcription and replication. The oscillations and waves or solitons extending on the DNA allow for activation of transcription by helping to incorporate energy into these areas. The looping that occurs in DNA during transcription is like breathing for DNA, i.e. a facilitating process, by folding of proteins and trajectory "bubbles" travelling down the DNA also carrying energy [39]. What are the energies involved in the oscillations and solitons? It appears to be greater than the biochemical and structural interactions incorporating only electromagnetic fields. It appears to be a synergism of multiple energies working in unison to allow efficient transcription in DNA [40,41].

Does function follow form in DNA transcription? New research will open doors for a better understanding of major and minor influences on transcription and gene regulation to open new doors for the development of cancer therapies, and offer a greater in depth understanding of the ability to manipulate the cell through this knowledge for greater advances in future medicine.

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