Non-Productive Pathways During Initiation Phase of RNA Transcription: Abortive and Antisense Transcription

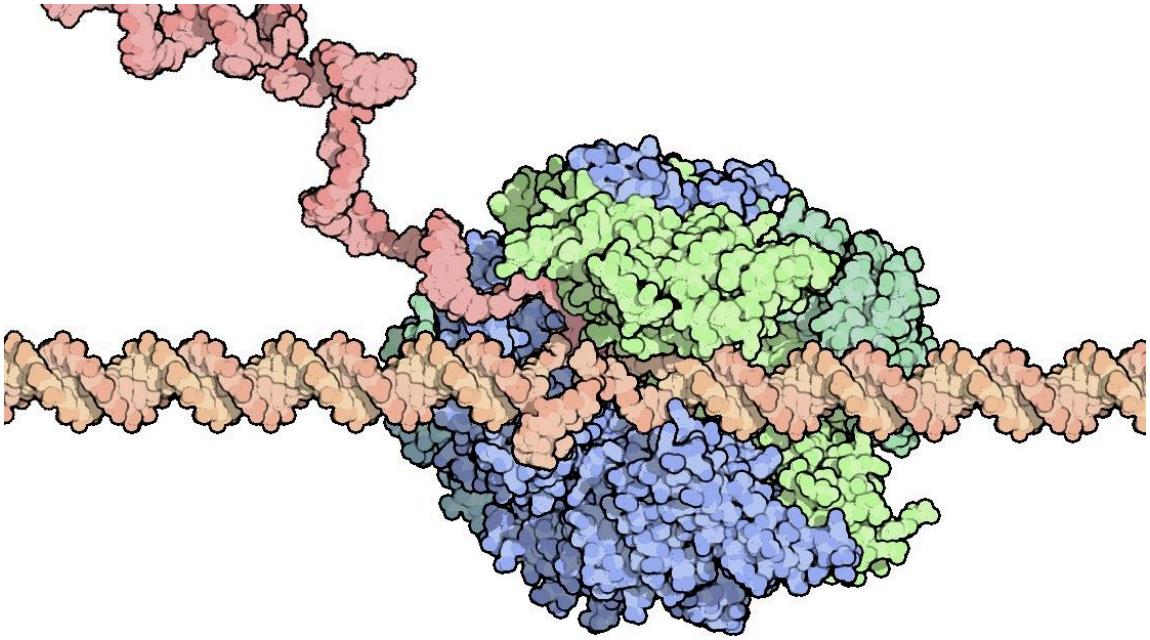

Figure 1. Model of Transcription of RNA using RNA Polymerase II

Note. From Molecule of the Month: RNA Polymerase, by D. S. Goodsell, 2003, RCSB PDB / PDB-101. https://pdb101.rcsb.org/motm/40. Copyright 2003 by RCSB PDB.

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INTRODUCTION

High school textbooks often present a highly simplified account of RNA transcription as the process through which messenger RNA (mRNA) is created: the DNA double helix unzips, unwinds, and exposes its bases to be copied. However, at a molecular level, this process is far more complex, involving multiple stages of initiation, elongation, and termination.

The scientific definition of RNA transcription is the process through which "a DNA sequence is enzymatically copied by an RNA polymerase to produce a complementary RNA" (Rice, 2007). Here, a new concept emerges: the enzyme RNA polymerase (RNAP), which catalyzes RNA synthesis. It is well-established in academic literature that RNAP is significantly more error-prone than DNA polymerase (Carey, 2015), which performs a nearly identical catalytic function (Alberts et al., 2002). This paper will introduce two cases that reflect the inherently low accuracy of the RNAP through separate mechanisms: the abortive and antisense transcription.

INITIATION PHASE

As mentioned above, RNA transcription progresses through three main phases: initiation, elongation, and termination. In particular, the initiation phase is a stepwise process in which the initial binding of RNAP to the promoter sequence induces conformational changes in both RNAP and the DNA. (Saecker et al., 2011)—here, the promoter sequence refers to a distinct region of DNA composed of a specific sequence of bases that signals to the RNAP to begin transcription (Deal et al., 2024). Upon initial binding, RNAP and the promoter sequence form a closed complex, in which the DNA remains double-stranded. Following promoter recognition, the DNA unwinds to form an open complex, also known as the initiation bubble (Saecker et al., 2011), within which RNAP begins RNA synthesis by copying the DNA template.

ABORTIVE INITIATION

During such processes, there is a high likelihood that RNAP may undergo abortive initiation. Abortive initiation can be defined as the "repetitive synthesis and release of short (..) RNAs by RNA polymerase" (Hsu, 2009) before productive initiation occurs. This can lead to the production of abortive products, which are composed of tiny fragments of RNA (Saecker et al., 2011). Although this frequent occurrence is well-characterized, its precise molecular mechanism remains unknown (Hsu, 2009). After multiple abortive initiations, the RNAP may successfully synthesise a transcript long enough (Heyduk & Heyduk, 2018). This enables the promoter escape, which is the "breaking of the favourable contacts between RNAP and the promoter," allowing the transcription process to transition into the elongation phase (Heyduk & Heyduk, 2018).

Like many mechanisms refined through evolutionary processes, abortive initiation exhibits distinct advantages that may outweigh its apparent inefficiency. For example, abortive transcription is often considered a crucial step in the initiation process as a potential error-checking mechanism that repetitively goes through "cycles of abortive synthesis" before the complex is fit for the production of successful transcripts (Henderson et al., 2019).

ANTISENSE INITIATION

Another, less universal phenomenon that occurs during transcriptional initiation is antisense transcription. This occurs when RNAP initiates at "promoters that are oriented in the opposite direction of genes" (Brophy & Voigt, 2016). Consequently, genetic information is transcribed from the template strand, which is the strand opposite the sense strand (Barman et al., 2019). The resulting antisense transcripts are therefore complementary to the target RNA transcript (Munroe & Zhu, 2006).

Like abortive initiation, this mechanism also exhibits functional significance beyond its apparent irregularity. This is exemplified by the regulatory roles antisense transcription plays in gene expression,

which involves controlling how much product is made, and when or where the production takes place (Pelechano & Steinmetz, 2013).

CONCLUSION

In conclusion, the two principal non-productive pathways RNA transcription can follow during the initiation phase shows the innate tendency of RNAP to stray from the canonical pathway of transcription. While these pathways are accompanied by functional advantages, they also present a significant challenge for large-scale RNA synthesis. Therefore, recent research is being directed at minimising unwanted side-products to ensure the industrial transcription can harness the full potential benefits. This is exemplified by methods related to engineered RNA polymerase with altered initiation properties (Sari et al., 2024) or the development of methods to remove unintended byproducts during RNA production (Cho et al., 2023). Looking ahead, by understanding the benefits and drawbacks of such processes, it may be possible to discover the most productive pathway of RNA transcription.

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