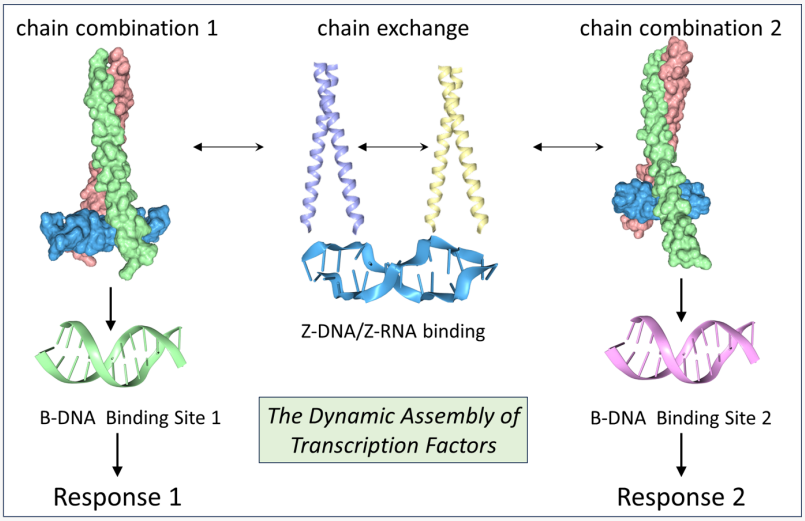
The Dynamic Targeting of Regulatory Proteins to Genes

Further Roles for Left-Handed Z-DNA in Gene Regulation



Transcription Factor chains bind to left-handed Z-DNA and Z-RNA structures formed by Active Genes. The exchange of chains on the Z-DNA surface generates new combinations that bind to different B-DNA sequences, activating site-dependent responses.

CHARLESTOWN, MA, UNITED STATES, December 30, 2025 / EINPresswire.com/ -- Combining parts in different ways can lead to product diversity. The challenge then becomes delivering the assembled product to the right location at the right time. Cells need to solve this problem to survive. In a paper just published in the International Journal of Medical Sciences titled "Control of Gene Expression by Proteins That Bind Many Alternative Nucleic Acid Structures Through the Same Domain" by Alan Herbert, a solution to the delivery problem is described. It relies on DNA's ability to form left-handed Z-DNA and four-stranded G-quadruplexes dynamically. These high-energy structures flag active genes and are genetically encoded by sequences called flipons.

The process occurs in three steps. First, each protein part is designed to pair with another, ensuring that they are correctly made. Second, the parts are delivered to genes flagged by the high-energy Z-DNA structure. The delivery system is the same for each pairing. Each pair is initially targeted to regions of Z-DNA formation, localizing them to the sites where the final assembled products will be needed. Third, the parts are reassembled to identify a pair combination that binds to a nearby gene control element. The reassembly occurs on the Z-DNA surface, and the optimal combination is determined through a trial-and-error process. Most pair combinations will not find anything to bind. These pairs are recycled to create new combinations. These pairs that do bind are stale when bound to the gene control system. They accumulate in the region and then

> The new generation of predictive modeling tools are really powerful"
>
> *Alan Herbert*

control gene expression.

In this way, cells can discover the best pairing of parts. There is no need to genetically pre-specify the best pair, as there are too many combinations to encode them all in advance. The combinations are instead selected from those parts available at the time. The selection can vary across cell types and tissues, enabling each to run different genetic programs as the context changes. The system is self-optimizing, as over time weak-binding pair combinations will be replaced by those that bind more strongly. The paper gives examples of this pairing process, involving Yamanaka factors in cellular reprogramming and proteins such as MYC that promote cancer.

The paper captures how our understanding of cells is dramatically changing. We are moving beyond models based solely on the right-handed B-DNA conformation described by Watson and Crick. Instead, current research focuses on how dynamical changes in DNA and RNA structures affect cell biology and disease processes. These advances have been enabled by the massive investment in the Human Genome Project and technological advances that allow analysis of the massive datasets produced. The progress is exemplified by the new appreciation of the role of the genome's repetitive elements. These elements were once considered non-informative because, as B-DNA, each repeat is so frequent. However, flipons are only encoded by repeat sequences. By changing their structure, flipons can switch on different pathways. This is exemplified by cellular Z-DNA and Z-RNAs that regulate immune responses against viruses.

InsideOutBio is a start-up focused on developing a novel class of proprietary therapeutics to ‘light up tumors for the immune system. These statements about InsideOutBio comply with the Safe Harbor laws. They are forward-looking and involve known and unknown risks and uncertainties. They are not guarantees of future performance, and undue reliance should not be placed on them.

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