Optimizing DNA nanostructures' design to advance targeted gene delivery

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Abstract

Targeted delivery of therapeutic agents to specific cellular compartments significantly enhances the efficacy and specificity of the treatments. This strategic approach reduces the likelihood of off-target effects, thereby minimizing potential side effects while increasing the overall therapeutic effectiveness. The use of self-assembled nucleic acids in this context is particularly noteworthy, as it enables the precise folding of DNA into complex structures tailored for targeted applications in nanotechnology. These engineered structures provide a safer alternative to conventional viral and bacterial vectors, facilitating non-integrating gene manipulation techniques essential for effective gene delivery.

The introduction of functional nanostructures into cellular environments is pivotal for myriad applications, necessitating precise control over the topology of these constructs. Such control is expertly achieved through the self-assembly process of DNA origami, a method underpinned by structural DNA nanotechnology. For the creation of intricate 3D DNA origami nanostructures, the MENDEL (Model ENfolded DNA Editing Library) software emerges as a critical tool. This advanced computer-aided design (CAD) library facilitates complex geometric modeling via a script-only interface, greatly simplifying the initial stages of design. It employs Python for detailed parametric designs, automates the calculation of staples, and produces files compatible with Cadnano. Additionally, it integrates with Blender to provide real-time visualization of the nanostructures, enhancing the overall design workflow. MENDEL software substantially streamlines the creation of complex DNA nanostructures, making the process more efficient and less time-consuming.

By simplifying the design process, MENDEL makes designing intricate DNA origami structures more accessible to researchers. Once assembled, these structures can be meticulously analyzed using Atomic Force Microscopy (AFM) to assess their size, shape, and structural integrity. Following these evaluations and necessary modifications to their surface and targeting mechanisms, DNA origami structures are strategically delivered into cells. This precise delivery ensures that the nanostructures reach their specified destinations within the cellular matrix, optimizing their functional impact and advancing the capabilities of targeted gene therapy.

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References:

Zadegan, R.M.and W.L.Hughes, CAGE: Chromatin Analogous Gene Expression. ACS Synthethic Biology, 2017.6(10):p.1800-1806.

Zhang,Y.,et al., Advanced application of DNA nanostructures dominated by DNA origami in antitumor drug delivery. Fron Mol Biosci, 2003.10:p.1239952.

Koh, H., et al. Design Approaches and Computational Tools for DNA Nanostructures. IEEE Open J Nanotechnol, 2021.2:p.86-100.