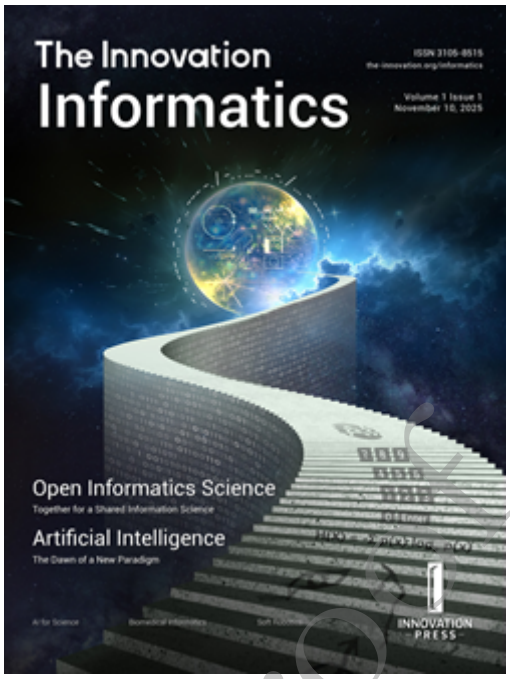

AI framework boosts precision of genome editing by harnessing AlphaFold3

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AI framework boosts precision of genome editing by harnessing AlphaFold3

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An artificial intelligence-driven framework developed by researchers at Peking University and East China Normal University has significantly improved the precision of DNA base editing, offering a new strategy to reduce unwanted off-target effects while maintaining high editing efficiency.

The study, "Precise DNA base editing using AlphaFold3-based contact modelling", was published in Nature on July 22.[1]

Base Editors (BEs) have become indispensable tools for both biological research and the development of gene therapies. However, improving their specificity without compromising editing activity has remained one of the field's most persistent challenges. Although several groups have attempted to leverage artificial intelligence to optimize genome editors, the effectiveness of such approaches has been uncertain.

To address this problem, a research team led by Yin Chengqi from School of Life Sciences, State Key Laboratory of Gene Function and Modulation Research, Beijing Advanced Center of RNA Biology (BEACON), Peking University and one led by Li Dali from East China Normal University's School of Life Sciences, turned to AlphaFold3, the latest AI model for predicting biomolecular structures. They used the model to analyze DNA-RNA-protein complexes formed by base editors at both intended (on-target) and unintended (off-target) genomic sites.

The researchers found that AlphaFold3's predicted three-dimensional structures often failed to capture the subtle conformational changes caused by single-base mismatches. In contrast, another output generated by the model, namely contact probability (CP) that estimates the likelihood that any two amino acid or nucleotide residues interact in close proximity, proved highly sensitive to these structural differences (Figure 1).

Systematic benchmarking further demonstrated that CP could reliably detect not only local conformational changes induced by single-base mismatches, but also interaction changes resulting from single amino acid substitutions. The findings suggested that CP provides a much more informative signal for distinguishing on-target from off-target interactions than structural predictions alone.

Building on this insight, the researchers integrated CP with high-throughput genome-wide off-target sequencing data to develop ContactSeek, an AI-driven framework that identifies interaction differences between on-target and off-target editing complexes. The framework pinpoints amino acid residues that play critical roles in determining editing specificity, providing a rational guide for protein engineering.

Using ContactSeek, the team successfully identified a series of novel Cas9 variants capable of substantially improving the precision of Adenine Base Editors (ABEs). The engineered variants maintained robust on-target editing while significantly reducing unintended DNA edits.

The researchers then extended the framework to optimize the deaminase component of base editors in order to minimize RNA off-target effects. By modeling deaminase-RNA complexes using RNA off-target sequencing data, ContactSeek identified additional amino acid residues that influence RNA editing specificity.

Combining the best-performing Cas9 variant with an optimized deaminase variant, the researchers created a new adenine base editor, ABE8e-DD. Compared with three leading high-fidelity adenine base editors currently available, ABE8e-DD preserved strong on-target editing activity while exhibiting substantially lower off-target editing at both the DNA and RNA levels.

The framework also demonstrated broad applicability. Applying ContactSeek to a Cas12a-A3A cytosine base editor similarly improved its editing specificity, suggesting the method can be generalized across multiple classes of genome-editing systems.

Beyond improving genome-editing tools, the study highlights a broader potential application of AlphaFold3. Rather than serving solely as a platform for predicting three-dimensional molecular structures, the model also contains rich internal molecular representations that can reveal subtle changes in biomolecular interactions. According to the researchers, this shifts AlphaFold3's role from simply predicting what molecules look like toward quantifying how their interactions change.

As artificial intelligence increasingly moves beyond the digital domain into the physical and life sciences, the study offers a new paradigm for integrating structural prediction with functional data to guide the rational design of more precise genome-editing technologies.

The researchers said the work not only provides a powerful framework for analyzing and optimizing biomolecular interaction specificity, but also underscores the importance of developing AI systems for life sciences that are both interpretable and experimentally verifiable, paving the way for safer and more precise biomedical applications.

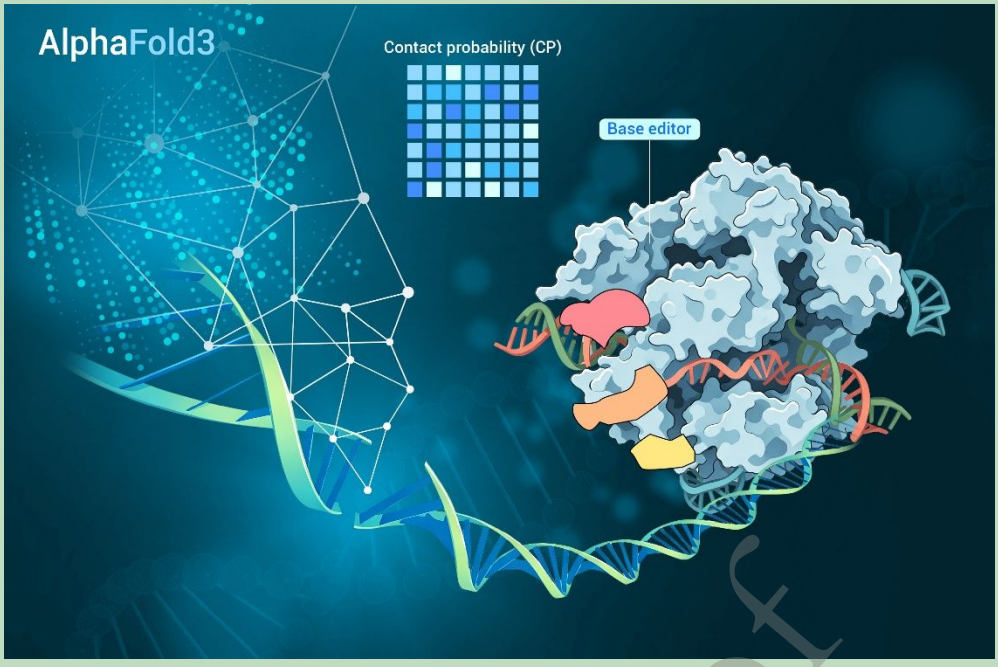

Figure 1. Illustration of the ContactSeek framework.

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DECLARATION OF INTERESTS

All authors declare no conflicts of interest.