

Proposal for PhD Research: Quantifying the Uncertainty in both On and Off-target Activity of Prime Editing

My previous work on the master's thesis focused on the on target prediction of prime editing efficiency, however, the off-target activity of prime editing is still a major concern.

With the recent development of a number of off-target site detection protocols supporting prime editors, it is now possible to quantify their off target activity using big data and deep learning techniques[1, 2].

Although majority of the existing solution (including my master's thesis) was aiming at producing a point estimation as the predicted editing efficiency[3, 4, 5], prime editing itself must be viewed as a stochastic process due to the physical complexity of the molecular interactions involved. Thus, instead of producing a point estimation, it could be more informative to model the posterior distribution of the activity of prime editing given the target loci and pegRNA sequence.

A reasonable starting point would be to investigate
Some preliminary study has been done on the
MC dropout/Deep ensemble

References

- [1] Shun-Qing Liang et al. "Genome-Wide Profiling of Prime Editor off-Target Sites in Vitro and in Vivo Using PE-tag". In: *Nature Methods* 20.6 (June 2023), pp. 898–907. ISSN: 1548-7105. DOI: 10.1038/s41592-023-01859-2. URL: <https://www.nature.com/articles/s41592-023-01859-2> (visited on 09/30/2024).
- [2] Ming Zhu et al. "Tracking-Seq Reveals the Heterogeneity of off-Target Effects in CRISPR–Cas9-mediated Genome Editing". In: *Nature Biotechnology* (July 2, 2024), pp. 1–12. ISSN: 1546-1696. DOI: 10.1038/s41587-024-02307-y. URL: <https://www.nature.com/articles/s41587-024-02307-y> (visited on 09/28/2024).

- [3] Nicolas Mathis et al. “Machine Learning Prediction of Prime Editing Efficiency across Diverse Chromatin Contexts”. In: *Nature Biotechnology* (June 21, 2024), pp. 1–8. ISSN: 1546-1696. DOI: 10.1038/s41587-024-02268-2. URL: <https://www.nature.com/articles/s41587-024-02268-2> (visited on 06/23/2024).
- [4] Goosang Yu et al. “Prediction of Efficiencies for Diverse Prime Editing Systems in Multiple Cell Types”. In: *Cell* 186.10 (May 2023), 2256–2272.e23. ISSN: 00928674. DOI: 10.1016/j.cell.2023.03.034. URL: <https://linkinghub.elsevier.com/retrieve/pii/S0092867423003318> (visited on 05/03/2024).
- [5] Jonas Koeppel et al. “Prediction of Prime Editing Insertion Efficiencies Using Sequence Features and DNA Repair Determinants”. In: *Nature Biotechnology* 41.10 (Oct. 2023), pp. 1446–1456. ISSN: 1087-0156, 1546-1696. DOI: 10.1038/s41587-023-01678-y. URL: <https://www.nature.com/articles/s41587-023-01678-y> (visited on 02/07/2024).