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Abstract

Motivation: Text Text Text Text Text Text.
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Contact: name@bio.com
Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRIPSR-associated protein 9 (Cas9) systems is preferred over other biological research and human medicine technologies now, beacuse of it's efficiency, robustness and programmability. Cas9 nucleases can be directed by short guide RNAs (sgRNAs) to introduce site-specific DNA double-stranded breaks in target, so to enable editing site-specific within the mammalian genome (Jinek *et al.*, 2012; Cong *et al.*, 2013; Mali *et al.*, 2013). CRISPR/Cas9, to a large extent, has developed genetic therapies at the cellular level, while there are still severe medical disadvantage even now which has greatly hindered the further clinical application of the CRISPR/Cas9 systems. One of these disadvantage is due to point mutations caused by off-target effects (Rubeis and Steger, 2018; Kang *et al.*, 2016; Ishii, 2017; Liang *et al.*, 2015). To overcome this disadvantage, a solution is to engineer CRISPR/Cas9 with higher specificities. That's why more and more higher specificities Cas9 variants, such as enhanced SpCas9 (eSpCas9(1.1)), Cas9-High Fidelity (SpCas9-HF1) (Ishii, 2017; Slaymaker *et al.*, 2016), hyper-accurate Cas9 (HypaCas9) (Kleinstiver *et al.*, 2016), been developed and bring a significant volume of experimental data, that is to say researchers have to face the difficulty of analyzing such huge and heterogeneous data.

The activity of chosen sgRNA sequence determines the success of genome editing, however distinctly fluctuant behaviors have been observed for the performance of different sgRNAs, even in the same Cas9 system. Some optimum sgRNAs can hit almost all targers alleles, while anothers don't even show activity (Wang *et al.*, 2019). This fact indicates that it's meaningful to explore an efficient method to guide sgRNA design. In practice, there have been a number of application and toolkit applied in this task. In the earlier studies, methods in silico are categorized into three types: (1) alignment-based, (2) hypothesis-driven and (3) learning-based (Chuai *et al.*, 2018). Recently we noticed that the last type of method seems to be getting more attention because of huger and huger data set (Liu *et al.*, 2019a). Learning-based method, which designed to predict the activity of sgRNAs, is essentially a computational model built by machine learning algorithm, not only conventional machine learning but also deep learning algorithm. Some studies on HT_ABE and HT_CBE have shown that deep learning based models often outperformed conventional machine learning, when the number of sgRNAs in the data set reached a certain level (Song *et al.*, 2020; Kim *et al.*, 2018, 2019). Per contra, conventional machine learning algorithms, such as linear regression, logistic regression and the decision tree, are often more interpretable due to the fewer parameters and clearer mathematical assumptions. In short, what was needed for developer is to trade-off accuracy and interpretability. Muhammad Rafidet al. consider deep-learning-based models as black boxs and believe they lack interpretability, motivated by the empirical assertion, they turn to build a model based conventional machine learning to compete with state of the art deep learning models (Muhammad Rafid *et al.*, 2020). On the other hand, input perturbation based feature importance analysis become a preferred components to reveal the importance of features in deep learning models. Liu et al. use a sliding window of length 2 to extract dimeric as input and rank the position of dimeric by contribution to final output (Liu *et al.*, 2019b). One regret is that subject to the processing of the input sgRNA sequence, their analysis can not exactly on the nucleotide class. Further, SHAP, one of the most prominent of model explain techniques, has been widely used to understand the decision made by the model. Wang et al. develope DeepHF, a deep learning based model, and use

Deep SHAP to revealed nucleotide contributions (Wang *et al.*, 2019). Deep SHAP is a compositional approximation of SHAP values since it is challenged to computate SHAP values exactly, especially for a complex deep neural networks (Lundberg and Lee, 2017). In our understanding, the method based on input perturbation often requires better generalization ability of the model (even for artificial ridiculous noise data). Moreover, recent work indicates that model explain techniques, which based post hoc explanations techniques and input perturbations, could be fooled to generate meaningless explanations instead of reflecting the underlying biases (Slack *et al.*, 2019), in other word, they could be unreliable and misleading, even on model with excellent performance. In light of the above, we believe it is essential to develope a model which can not only match deep learning based model in performance, but also be comparable to conventional machine learning algorithms in interpretability.

2 Approach

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3 Methods

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Fig. 1. Caption, caption.

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4 Discussion

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5 Conclusion

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Acknowledgements

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References

Bauer, M., Klau, G. W., and Reinert, K. (2007). Accurate multiple sequence-structure alignment of RNA sequences using combinatorial optimization. *BMC Bioinformatics*, **8**, 271.

Chuai, G., Ma, H., Yan, J., Chen, M., Hong, N., Xue, D., Zhou, C., Zhu, C., Chen, K., Duan, B., *et al.* (2018). Deepcrispr : optimized crispr guide rna design by deep learning. *Genome Biology*, **19**(1), 1–18.

Cong, L., Ran, F. A., Cox, D. D., Lin, S., Barretto, R. P. J., Habib, N., Hsu, P., Wu, X., Jiang, W., Marraffini, L. A., *et al.* (2013). Multiplex genome engineering using crispr/cas systems. *Science*, **339**(6121), 819–823.

Ishii, T. (2017). Reproductive medicine involving genome editing: clinical uncertainties and embryological needs. *Reproductive Biomedicine Online*, **34**(1), 27–31.

Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., and Charpentier, E. (2012). A programmable dual-rna-guided dna endonuclease in adaptive bacterial immunity. *Science*, **337**(6096), 816–821.

Kang, X., He, W., Huang, Y., Yu, Q., Chen, Y., Gao, X., Sun, X., and Fan, Y. (2016). Introducing precise genetic modifications into human 3pn embryos by crispr/cas-mediated genome editing. *Journal of Assisted Reproduction and Genetics*, **33**(5), 581–588.

Kim, H. K., Min, S., Song, M., Jung, S., Choi, J. W., Kim, Y., Lee, S., Yoon, S., and Kim, H. (2018). Deep learning improves prediction of crispr-cpf1 guide rna activity. *Nature Biotechnology*, **36**(3), 239–241.

Kim, H. K., Kim, Y., Lee, S., Min, S., Bae, J. Y., Choi, J. W., Park, J., Jung, D., Yoon, S., and Kim, H. (2019). Spcas9 activity prediction by deepspcas9, a deep learning–based model with high generalization performance. *Science Advances*, **5**(11).

Kleinstiver, B. P., Pattanayak, V., Prew, M. S., Tsai, S. Q., Nguyen, N. T., Zheng, Z., and Joung, J. K. (2016). High-fidelity crispr–cas9 nucleases with no detectable genome-wide off-target effects. *Nature*, **529**(7587), 490–495.

Liang, P., Xu, Y., Zhang, X., Ding, C., Huang, R., Zhang, Z., Lv, J., Xie, X., Chen, Y., Li, Y., *et al.* (2015). Crispr/cas9-mediated gene editing in human tripronuclear zygotes. *Protein & Cell*, **6**(5), 363–372.

Liu, G., Zhang, Y., and Zhang, T. (2019a). Computational approaches for effective crispr guide rna design and evaluation. *Computational and structural biotechnology journal*, **18**, 35–44.

Liu, Q., He, D., and Xie, L. (2019b). Prediction of off-target specificity and cell-specific fitness of crispr-cas system using attention boosted deep learning and network-based gene feature. *PLoS computational biology*, **15**(10), e1007480–e1007480. 31658261[pmid].

Lundberg, S. and Lee, S. (2017). A unified approach to interpreting model predictions. pages 4768–4777.

Mali, P., Yang, L., Esvelt, K. M., Aach, J., Guell, M., Dicarlo, J. E., Norville, J. E., and Church, G. M. (2013). Rna-guided human genome engineering via cas9. *Science*, **339**(6121), 823–826.

Muhammad Rafid, A. H., Toufikuzzaman, M., Rahman, M. S., and Rahman, M. S. (2020). Crisprpred(seq): a sequence-based method for sgrna on target activity prediction using traditional machine learning. *BMC Bioinformatics*, **21**(1), 223.

Rubeis, G. and Steger, F. (2018). Risks and benefits of human germline genome editing: An ethical analysis. *Asian Bioethics Review*, **10**(2), 133–141.

Slack, D., Hilgard, S., Jia, E., Singh, S., and Lakkaraju, H. (2019). Fooling lime and shap: Adversarial attacks on post hoc explanation methods. *arXiv: Learning*.

Slaymaker, I. M., Gao, L., Zetsche, B., Scott, D. A., Yan, W. X., and Zhang, F. (2016). Rationally engineered cas9 nucleases with improved specificity. *Science*, **351**(6268), 84–88.

Song, M., Kim, H. K., Lee, S., Kim, Y., Seo, S.-Y., Park, J., Choi, J. W., Jang, H., Shin, J. H., Min, S., Quan, Z., Kim, J. H., Kang, H. C., Yoon, S., and Kim, H. H. (2020). Sequence-specific prediction of the efficiencies of adenine and cytosine base editors. *Nature Biotechnology*.

Wang, D., Zhang, C., Wang, B., Li, B., Wang, Q., Liu, D., Wang, H., Zhou, Y., Shi, L., Lan, F., *et al.* (2019). Optimized crispr guide rna design for two high-fidelity cas9 variants by deep learning. *Nature Communications*, **10**(1), 4284–4284.