IZKF Research Group Bioinformatics
Computational Biology Division

Institute for Biomedical Engineering
RWTH Aachen University Medical School

Aachen Institute for Advanced Study in
Computational Engineering Science
RWTH Aachen University

Ivan G. Costa, PhD
Pauwelsstrasse 19 • 52074 Aachen, Germany
Tel.: +49-241-80 80270
www: http://www.costalab.org

Dear Dr. Rusk,

Thank you very much for your email on May 6, 2015 regarding our paper by Gusmao et al., "Correction of DNase-seq cleavage bias impacts on quality of footprinting" (NMETH-C24264). We would like to thank you and the Reviewers for the thorough review of our paper and the constructive comments.

We have included in our analysis the requested transcription factors and DNase-seq experiments and expanded our evaluation with additional footprinting methods. Our study is the most comprehensive benchmarking evaluation of methods for DNase-seq analysis produced so far. Novel analysis further corroborate with our previous manuscript that signal correction improves footprint predictions. We observe that cleavage bias only influence the predictive performance of half of the footprint methods analyzed. Moreover, the inclusion of bias correction on our footprinting method (HINT) leads to the best accuracy performance.

Following reviewers requests, our manuscript includes now an analysis of cleavage bias on TFs with short binding time. We observe that footprinting methods have poor predictive performance for these factors and that no clear footprint shape can be detected even after bias correction. We propose, therefore, a statistical measure (protection score) to computationally identify TFs with short binding time from footprint predictions and motif-predicted binding sites alone. The proposed score can successfully discriminate TFs with short, intermediate and long binding times and significantly correlates with the performance of footprint methods.

Finally, to accommodate the inclusion of requested additional analysis and reviewer 2 criticism on the current format, we have changed our manuscript format to a "Brief Communication". We believe that our analysis addresses important concerns raised in He et al. study. Moreover, our methodological advances, which include a method for bias correction and detection of short time binding factors, significantly improve the footprint detection problem.

We would appreciate very much if you would consider our Brief Communication for publication in Nature Methods. In addition, we should be happy to answer any further question, which you might have.

With best regards,

Ivan G. Costa
Computational Biology Division
Institute for Biomedical Engineering
RWTH Aachen University