## General comments

The manuscript by Oberbeckmann et al. presents a survey of absolute nucleosomal occupancy in the yeast genome using a combination of restriction-enzyme and DNA methylation-based approaches for profiling accessible chromatin. Overall, this is a well written, detailed, thorough and carefully done study that adds new results and insights to the literature, and that will be of interest to readers. There are, however, a few issues with the current version of the text that should be corrected or clarified before it can be accepted for publication.

## Specific comments

1. Saturation of accessible chromatin methylation can be achieved in two ways. One is incubating with enzyme for a long time, which is the approach adopted by the authors. The other is to use high doses of highly concentrated enzymes. The latter is much preferable as it avoids the possible side effects of prolonged incubation of chromatin.

2. The coverage bias issue is not quite fully explained in my opinion. The effects of bisulfite conversion are waved away as not a concern. However, it is in fact at this point very strongly suspected that bisulfite conversion does in fact result in significant coverage biases, as the conversion reaction destroys DNA (indeed, this is why there is no fragmentation step in bisulfite sequencing protocols); because they are conversion-dependent, these coverage biases are likely also to an extent methylation level-dependent too. This has been one of the primary motivations behind developing alternative methods such as EM-seq. On the other hand, of course, the coverage bias is also present in the BamHI + $MgCl_2$ sample shown in Figure S2D, and there is no RE data without magnesium (and there likely will not be as most RE enzymes require it), thus it is still possible that the otherwise similar effects in RE- and methylation-based accessible chromatin profiling arise from different sources.

3. Nanopore sequencing still has quite high error rates at the single-molecule level; even Nanopolish, which is as good a tool for calling CpG methylation as there is at the moment, returns a 10% or so false positive calls. Thus it is somewhat surprising that the authors claim to obtain nearly exactly the same results using nanopore sequencing as they do with bisulfite conversion plus Illumina sequencing given that no significant filtering or data conversion steps past the Nanopolish step are described regarding the nanopore analysis.

4. The transcription factor footprinting section could be expanded significantly to include more factors for which ChIP-seq/ChIP-exo datasets in *S. cerevisiae* are available.

5. While methylation-based approaches for mapping open chromatin are increasingly gaining traction, DNAse-seq, and especially ATAC-seq, are still the most popular methods for evaluating chromatin accessibility. It would be useful to compare the absolute occupancy results obtained by the authors with ATAC-seq datasets as such a comparison is currently missing from the paper. This is especially relevant to the section concerning occupancy/accessibility around highly transcribed genes, which right now present some counterintuitive results that go both against conventional wisdom and against anecdotal but still rather frequent observations of wide regions of accessibility (as measured by ATAC/DNAse-seq) in such regions.

6. It is not clear what exactly the difference between ODM-seq and NOMe-seq is. Some modifications are made to the protocol and the effects of different reaction conditions are explored, but there is nevertheless nothing fundamentally different between ODM-seq and NOMe-seq. To be noted, the dSMF paper from 2017, which used both CpG and GpC methyltransferase enzymes, did warrant a new name, because the combination of two enzymes had not been used previously. But that has also been already done, and in this case, only single enzymes were used in each reaction. It would be much better to refer to ODM-seq as "NOME-seq" in order to avoid introducing further confusion in the literature with multiple names referring to the same thing. Similarly, there are other, both recent and older, studies using restriction enzymes too.