An empirical study that demonstrates that this simple model really applies in this context would be desirable to justify the extrapolation. While we believe that incorporating epigenetic data, and other types of data, into mutation signatures is an important and exciting direction for future work, we also believe that a proper investigation of this will be a major undertaking and view it as a project in itself that is outside the scope of our current paper. We also believe that, even without this additional work, the combination of novel models, software and visualization tools that are included here already represent a substantive and important advance - one that will be of considerable interest to both methodological, and applied researchers, and perhaps, as reviewer 2 suggests, will dramatically change the way that mutational signatures are identified in practice.

One very clear example is that the Pol epsilon mutation signature, which puts strong probability masses on just two pattern (TpCpT > TpApT and TpCpG > TpTpG), identified as “Signature 10” in the previous literature (Alexandrov et al., Nature, 2013). and the frequencies of substitution patterns and bases at the +1 positions are not propotional unlike the APOBEC signature.

