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mapDamage2.0: fast approximate Bayesian estimates of ancient DNA damage parameters

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1 INTRODUCTION

DNA in historical samples is subject to a plethora of environmental conditions and degradation reactions (Sawyer et al., 2012). A basic site, strand breaks, interstrand cross-links and a wide diversity of atypic nucleotidic bases are formed following oxidative and hydrolytic degradation (Lindahl, 1993; Pääbo et al., 2004), even in the most favorable preservation conditions.

Post-mortem DNA damage limits our ability to access ancient DNA (aDNA) sequences and increases the risk of exogenous modern contamination, as undamaged DNA molecules are more prone to enzymatic manipulation. Nucleotide misincorporation patterns, which are mostly driven by deaminated forms of cytosines (uracils), have been suggested as a powerful approach to authenticate aDNA sequences generated on next-generation sequencing (NGS) platforms (Briggs et al., 2007) and motivated the creation of the mapDamage package (Ginolhac et al., 2011). Such patterns could vary according to the specific molecular approach used for constructing (Meyer et al., 2012) and/or amplifying (Ginolhac et al., 2011) second-generation DNA libraries. For instance, for one of the most popular protocols (Meyer and Kircher, 2010), we observe inflated cytosine deamination rates at 5’-overhangs, an increase in C → T substitution rates toward sequencing starts and complementary increase in G → A rates toward reads ends (Briggs et al., 2007). Conversely, a novel procedure targeting single-stranded templates has shown elevated C → T substitution rates at both ends (Meyer et al., 2012).

Statistical modeling of such patterns has been developed by Briggs et al., 2007 with strand break, overhangs and cytosine deamination as key factors. Using read alignment to reference genomes and maximum likelihood optimization, this approach has delivered the first quantitative estimates of damage parameters. However, the likelihood framework originally implemented scales poorly with the size of NGS datasets, and extensive running times have prevented common usage. Here, we present an extension of mapDamage, which implements a fast approximation of the DNA damage model using a Bayesian framework. mapDamage 2.0 opens the possibility of comparing DNA damage levels across temporal and environmental gradients. Posterior distributions of damage parameters also enable penalizing the quality score of likely damaged bases, reducing noise in downstream single-nucleotide polymorphism (SNP) calling procedures.

2 APPROACH

Here we build on the DNA damage model described in Briggs et al., 2007. We make the simplifying assumption that mutations...
and post-mortem DNA damage are independent within a fragment, with occurrences depending only on the relative position from the sequence ends.

3 METHODS

The general idea is to mutate bases following an Hasegawa, Kishino and Yano (HKY) transition matrix (Hasegawa et al., 1985) and then independently add post-mortem damage on top of mutated bases. In this framework, we have multinomial distributions describing the position-specific substitutions for any given base \(S_{A,i} \sim \text{Mul}(D_{A,i}(1, 0, 0, 0) \cdot \Theta(\mu, \rho) \cdot p_{\text{dam}}(\delta, \delta, \lambda, v, i))\).

\(\Theta\) is the HKY transition matrix, and \(p_{\text{dam}}\) is defined as the DNA damage transition matrix. We assume post-mortem cytosine deamination is the main driver of nucleotide misincorporations in agreement with experimental evidence (Briggs et al., 2007), providing

\[
p_{\text{dam}} = \begin{pmatrix}
1 & 0 & 0 & 0 \\
0 & 1 - p_{\text{ct}} & 0 & p_{\text{ct}} \\
p_{\text{gt}} & 0 & 1 - p_{\text{gt}} & 0 \\
0 & 0 & 0 & 1
\end{pmatrix}
\]

Where the base-specific damage probabilities are defined as

\[
p_{\text{ct}}(\delta, \delta, \lambda, v, i) = v(\lambda \delta + \delta(1 - \lambda))
\]

\[
p_{\text{gt}}(\delta, \delta, \lambda, v, i) = (1 - v)(\lambda \delta + \delta(1 - \lambda))
\]

The motivation for the base-specific damage probabilities \(p_{\text{dam}}\) is best explained by the Markov chain in Figure 1 where the first jump decides if the position is before or after a nick; then a C \(\to\) T substitution could be observed following deamination in overhang or double-stranded DNA regions. A similar Markov chain could be drawn for G \(\to\) A substitutions (Supplementary Section 1).

For rescaling base quality scores, we assume that C \(\to\) T and G \(\to\) A substitutions either originate from true biological differences or from damage driven misincorporations. We can derive an estimate for the probability that a C \(\to\) T (similar for G \(\to\) A) misincorporation at position \(i\) along the reads is due to damage using

\[
p_{\text{dam}}(i) = \frac{\Theta_{\text{c},c} \cdot P_{\text{c},c}(i)}{\Theta_{\text{c},c} \cdot P_{\text{c},c}(i) + \Theta_{\text{c},t}}
\]

We can now correct base quality scores provided in alignment BAM files \([p_{\text{ct}}(i, r) \text{ at position } i \text{ for read } r]\) using

\[
p'_{\text{ct}}(i, r) = 1 - (1 - p_{\text{ct}}(i, r))(1 - p_{\text{dam}}(i))
\]

4 DISCUSSION

We applied mapDamage2.0 on a series of aDNA sequence datasets generated from a range of periods, source materials and environments (Supplementary Section 3). Posterior predictive intervals and empirical frequencies are in general agreement, as shown for the ancient plague dataset (Supplementary Table S2 and Supplementary Figs S4–S9) (Schuenemann et al., 2011), demonstrating the adequacy of our method. We observed a ratio of cytosine deamination rates for double- and single-stranded regions orders of magnitude greater than estimates based on in vitro experiments in aqueous solution (0.007 in Lindahl, 1993 versus 0.026-0.070 for Schuenemann et al., 2011 in Supplementary Table S1). This suggests that tissue- and sample-specific micro-environmental characteristics drive different DNA damage kinetics in situ. We also found a significant rank correlation between the posterior mean for single-stranded cytosine deamination and sample age (Supplementary Table S3) in agreement with Sawyer et al., 2012. However, remains of similar age and location showed diverse parameter estimates (Supplementary Table S2), suggesting a prominent role of micro-environmental characteristics over age in diagenesis.

We also applied our quality rescaling scheme to the sequence data of an Australian Aboriginal individual who died in 1920s (Rasmussen et al., 2011). This increased the overlap of genotype calls to dbSNP v137, suggesting that lower false-positive SNP calls were achieved (Supplementary Table S4).

5 CONCLUSION

We have developed a computational method for inferring aDNA damage parameters from NGS sequence datasets, with minimal changes to the DNA damage model presented by Briggs et al., 2007. Our model is compatible with the specificities of different sequencing and library building protocols. We believe that downscaling quality scores of likely damaged bases is the first from a long list of possible applications for damage parameter posterior distributions, limiting the impact of nucleotide misincorporations in downstream sequence analyses. The knowledge of such distributions could also be instrumental for improving mapping procedures to reference genomes (Schubert et al., 2012).

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Conflict of Interest: none declared.
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