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## Supplementary information S1 (box) | **High fidelity DNA synthesis**

Accurate DNA replication is a fundamental requirement for genomic stability. Replicative DNA polymerases achieve remarkably high-fidelity with just one error occurring in ten billion base pairs duplicated. Such high fidelity is achieved in three distinct steps: accurate base selection; proofreading of errors generated; and post-replicative mismatch repair [1,2].

Correct base selection provides the largest single contribution to polymerase fidelity, with only one incorrect base incorporated in the region of every 100,000 base pairs replicated. The molecular structures of a number of polymerases and their complexes have been determined and these structures reveal that the polymerases include three subdomains that are associated with binding of the DNA primer template and an incoming dNTP, termed 'palm,' 'finger', and 'thumb' subdomains because of their resemblance to a right hand [3] (Fig. 2). The palm domain contains two conserved carboxylate residues that are required for the phosphoryl transfer reaction. High fidelity base selection is achieved through movement of the 'finger' domain. In the absence of nucleotide, the 'finger' are in a so-called 'open' conformation. Binding of a correct dNTP induces large changes in the position of the 'fingers' domain, as well as subtle changes in amino acid side chains and in DNA conformation. These dNTP-induced changes result in a 'closed' ternary complex containing a binding pocket that snugly surrounds the newly-formed base pair and an active site that is poised for catalysis. A wrong incoming dNTP generates a mismatched base pair that significantly inhibits both of these steps.

Misincorporations nevertheless occur, with the most frequent being the 'wobble' base, dG, opposite template T [4]. High-fidelity DNA polymerases contain another sub-domain that encodes a 3′-5′ exonuclease and rapid shuttling of the mispaired primer-template between the polymerase and exonuclease active sites leads to the efficient removal of the misincorporated base [5]. It is estimated that such 'proofreading' contributes another 100-fold to the accuracy of replication fidelity[1,2].

Last, but not least, any remaining errors are further 'sanitized' through post-replicative mismatch repair [6], with the latter adding yet another 1000-fold to the overall accuracy of genome duplication [1,2].


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