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Fluctuation and fidelity control of a non-proofreading polymerase

JIN YU, Beijing Computational Science Research Center — Polymerases catalyze gene replication and transcription. They modulate activation barriers of nucleotide incorporation and amplify maximal free energy differentiation between the right and wrong nucleotides. It is essential for the polymerases to achieve sufficiently high fidelity at sufficiently high speed. We had noticed a small free energy bias in the translocation of T7 RNA polymerase (RNAP) that aids nucleotide selection. We investigated further how polymerases select against wrong nucleotides efficiently with given kinetics for the right, and with controlled differentiation capacities. We found that early selections on the reaction path outperform the late ones in error reduction. In particular, initial screening seems indispensable for lowering error rates without lowering much the speed. To see how exactly the nucleotide selection proceeds, we studied T7 RNAP also in atomistic simulations. We found that substantial nucleotide selection happens early, prior to full insertion of the nucleotide for complete Watson-Crick base pairing. A highly conserved residue brings up the small translocation energy bias by marginally blocking the active site. The residue senses the nucleotide species upon the nucleotide pre-insertion, and selectively 'gates' the nucleotide during insertion. Our studies thus provide a kinetic survey of the nucleotide selection system along with underlying molecular mechanisms.

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