Supporting information for

Networked communication between polymerase and exonuclease active sites in human mitochondrial DNA polymerase

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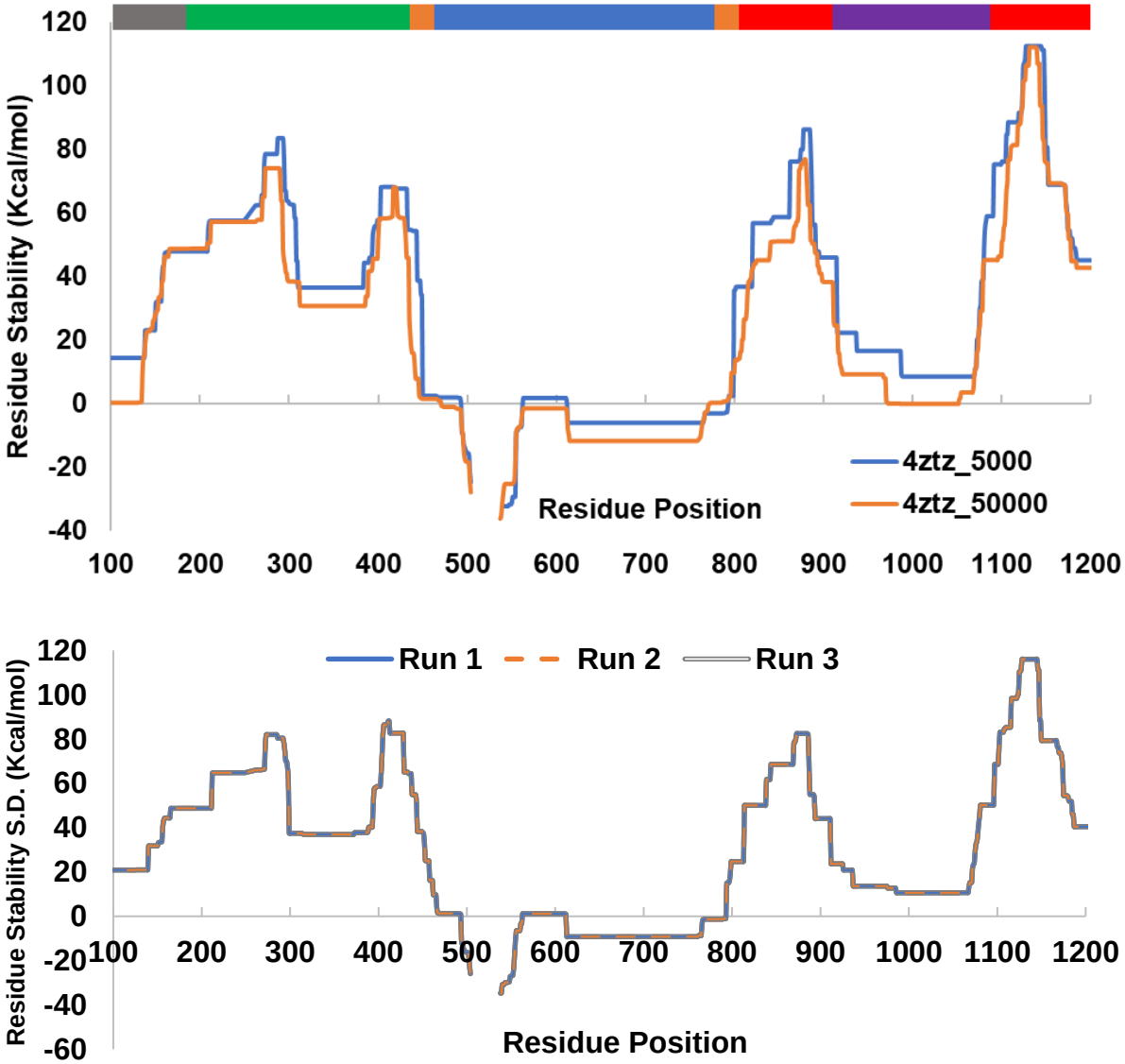
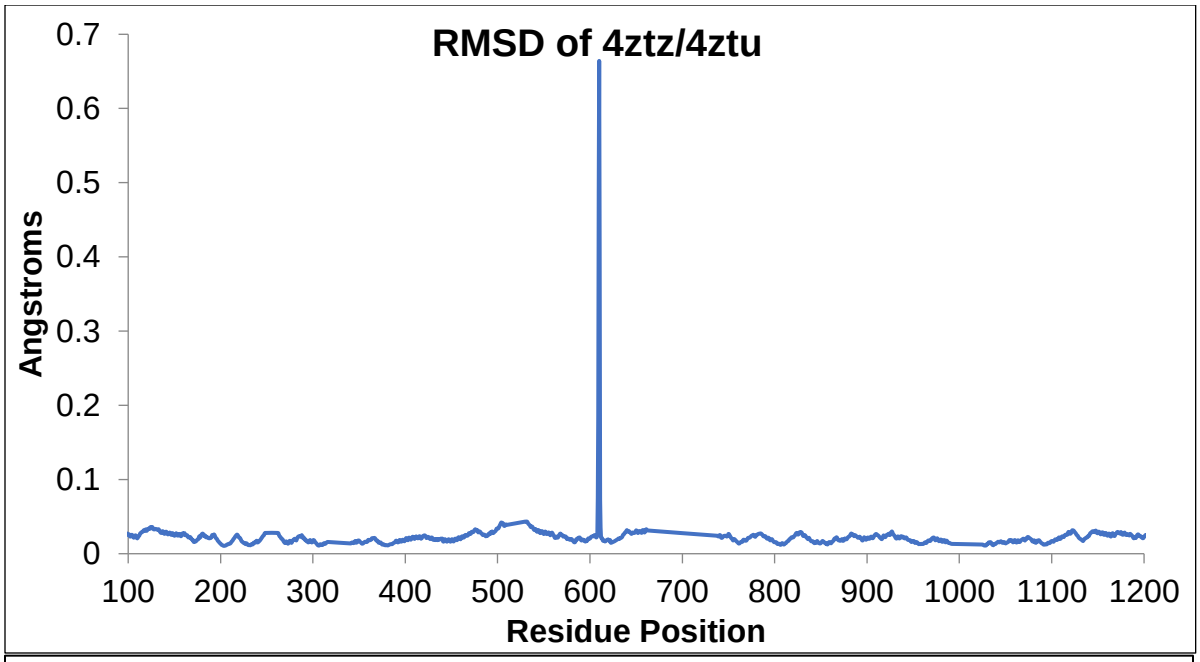


Figure S1. COREX Monte Carlo residue stability calculations are consistent at different conformational sampling sizes and multiple runs. (Top) dCTP containing structure run at two sampling sizes, 5000 and 50000 samples per partition, show that the results are consistent across sampling size. (Bottom) The same structure was run three separate times at the same settings (5000 samples) and show that conformational sampling is consistent across runs.



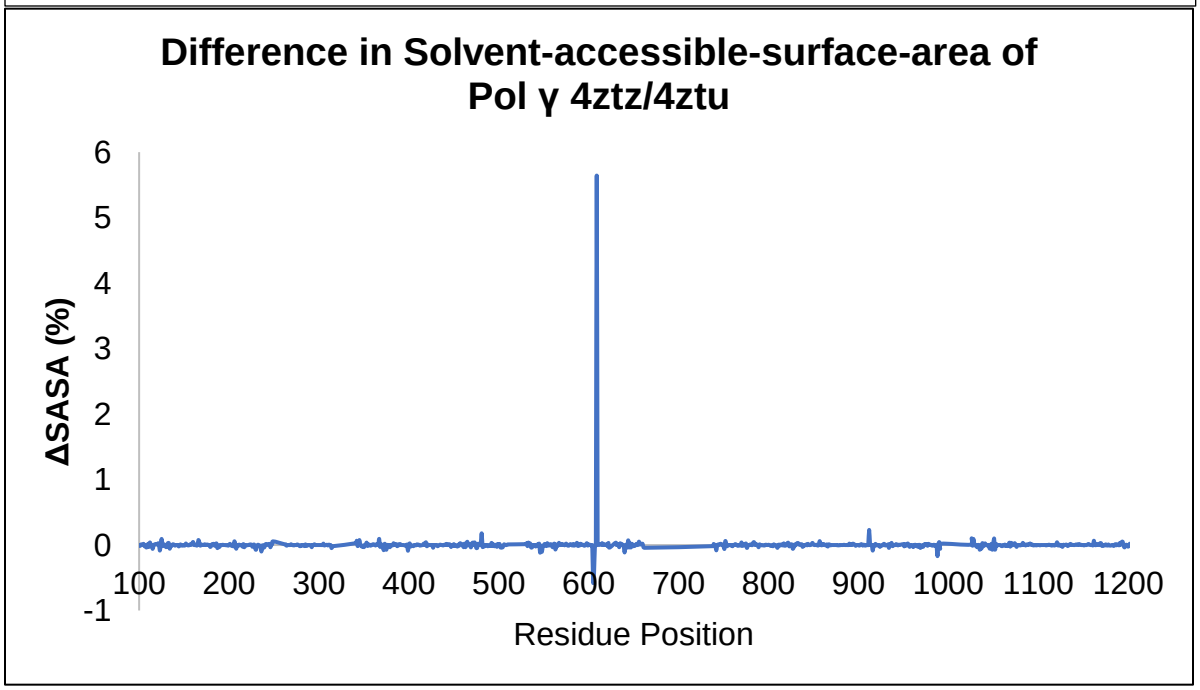


Figure S2. Differences in amino acid 3-dimensional positions as well as solvent-accessible-surface-area (SASA) of dCTP containing ternary complex (4ztz) optimally superimposed on the ddCTP containing structure (4ztu). Amino acids with missing atoms in 4ztu were converted into alanine prior to running COREX. Corresponding residues were also changed in 4ztz, as described in the Methods section. This figure demonstrates that there are appreciable but subtle differences between the two structures. The spike at residues 609/610 is the largest observed difference between the two crystal structures.

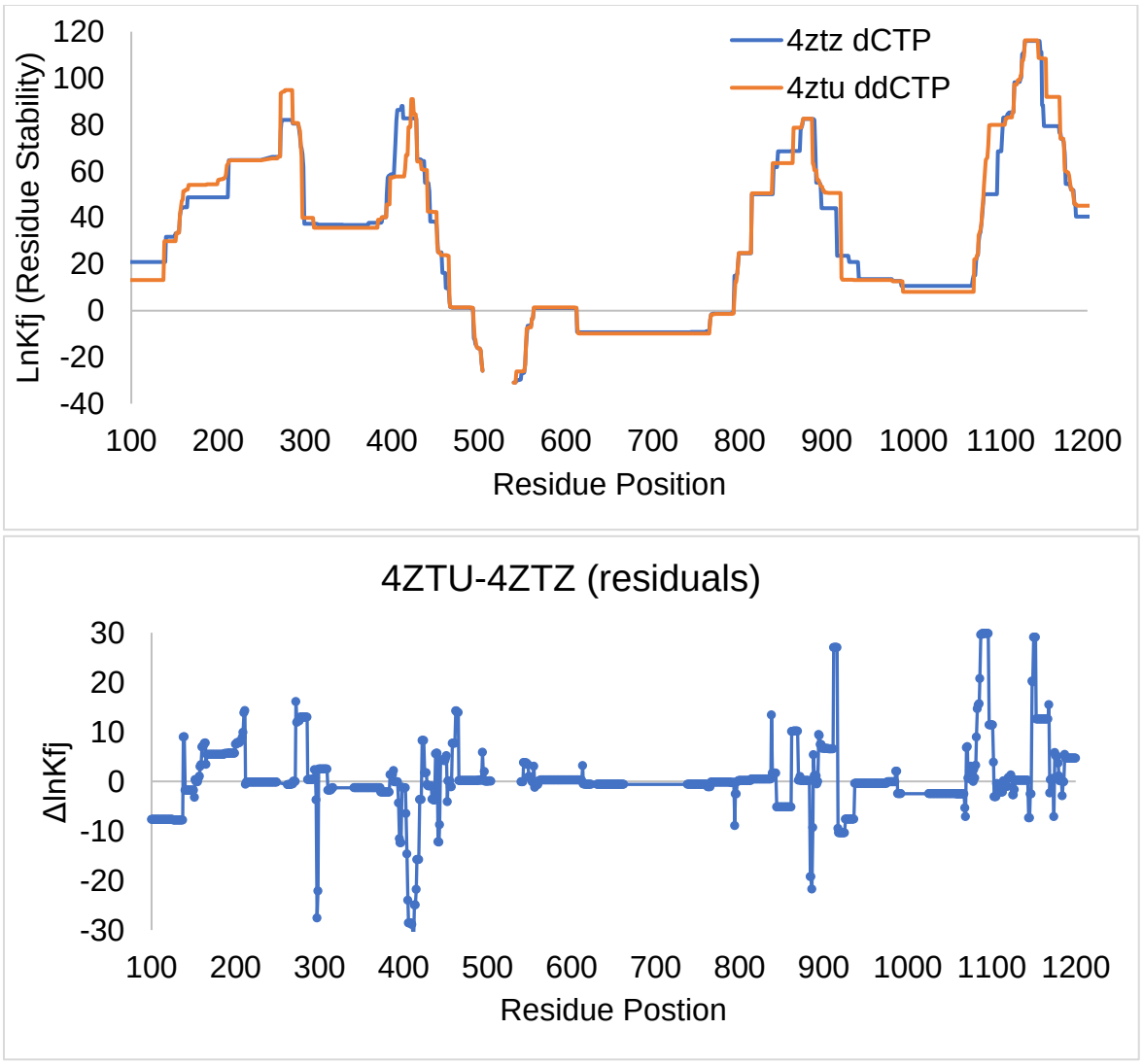


Figure S3. Residue Stability calculations of COREX Monte Carlo. (Above) Residue stability as calculated by COREX of the dCTP and ddCTP containing structures are plotted and show modest differences (4ztz, 4ztu). (Below) residuals of residue stability are shown to more clearly demonstrate the regional differences in residue stability. Small differences in local SASA are captured by COREX and the algorithm simulates propagation of local changes across the entire protein due to weighting microstate probabilities by their energetics using a partition function.

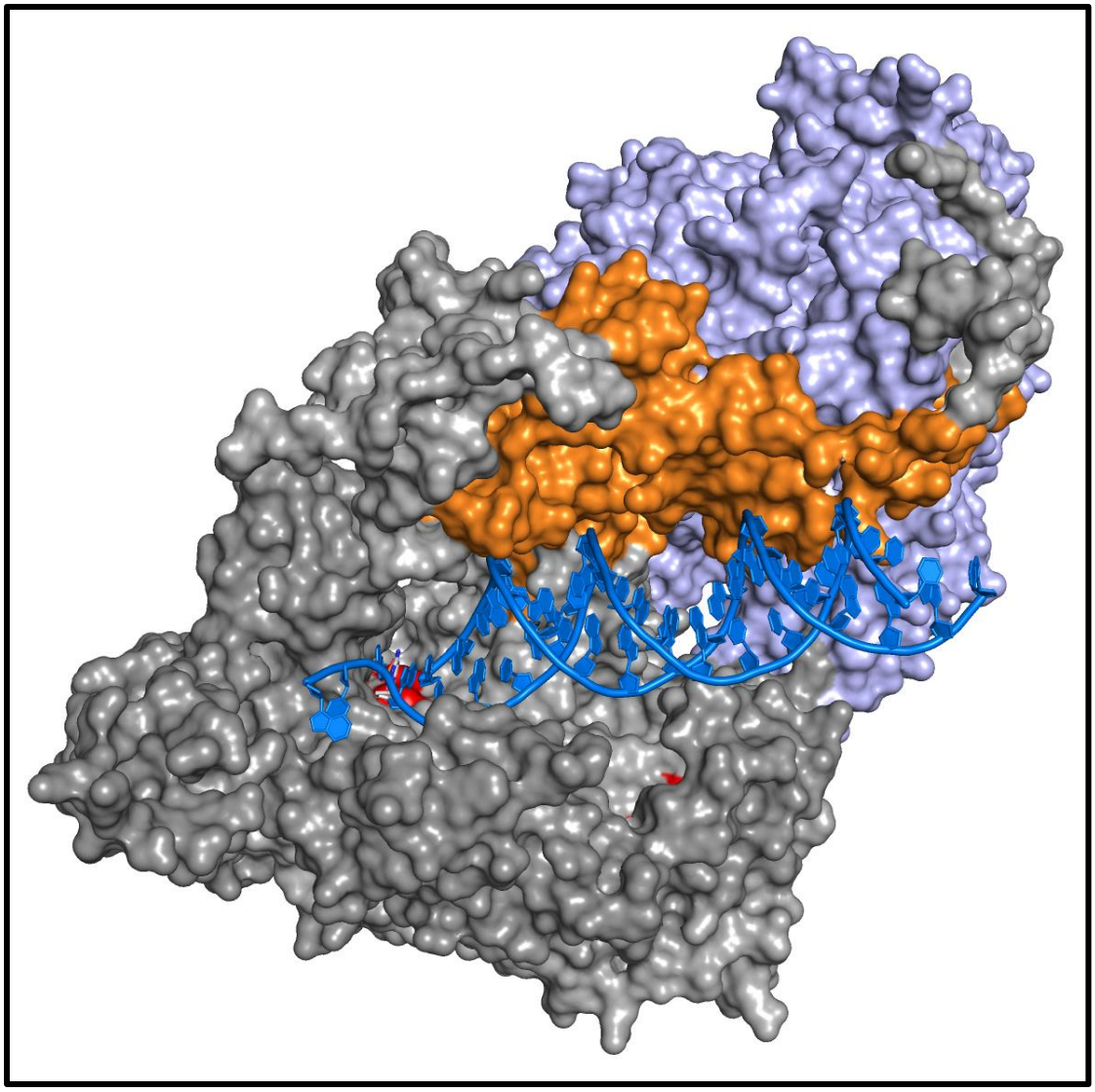


Figure S4. Diffusely cooperative residues directly interact with DNA and processivity subunits. Shown in orange are diffusely cooperative residues 450-500, 550-622, and 775-800, in gray Pol γA, in light blue the processive subunits Pol γB, in dark blue DNA, and active site residues in red.

PDB ID	Protein	DNA	dNTP analogues	Mutations
4ztz	pol γA/γB	24/28nt primer/template	dCTP	D198A D200A
4ztu	pol γA/γB	24/28nt primer/template	ddCTP	D198A D200A
5c52	pol γA/γB	24/28nt primer/template	(-)-FTC-TP	D198A D200A
5c53	pol γA/γB	24/28nt primer/template	(+)-FTC-TP	D198A D200A

Table S1. Crystal structures of Polymerase γ

PDB ID:	4ztz	4ztu	5c52	5c53
4ztz	-	0.019	0.246	0.240
4ztu	-	-	0.247	0.231
5c52	-	-	-	0.246
5c53	-	-	-	-

Table S2. Backbone RMSD differences between different complexes of Pol γ with identical DNA primer template but different substrates, suggesting that any structural differences between them are small. Units are Angstroms.

PDB ID:	Template/Primer Base Pair
1L3U	A:T
1NJW	G:T
1NJX	T:G
1NJY	T:T
1NJZ	C:T
1NK0	A:G
1NK4	G:G
1NK5	A:A
1NK6	C:C
1NK7	G:A

Table S3. Pol 1 BF crystal structures analyzed with COREX