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A structural and dynamical model of human telomerase

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Mutations in the telomerase complex disrupt either nucleic acid binding or catalysis, and are the cause of numerous human diseases. Despite its importance, the structure of the human telomerase complex has not been observed crystallographically, nor are its dynamics understood in detail. Fragments of this complex from Tetrahymena thermophila and, more controversially,Tribolium castaneum have been crystallized. Biochemical probes provide important insight into dynamics. In this work we use available structural fragments to build a homology model of human TERT, and validate the result with functional assays. We then generate a trajectory of telomere elongation following a "typewriter" mechanism: the RNA template moves to keep the end of the growing telomere in the active site, disengaging after every 6-residue extension to execute a "carriage return" and go back to its starting position. A hairpin can easily form in the telomere, from DNA residues leaving the telomere-template duplex. The trajectory is consistent with available experimental evidence and suggests focused biochemical experiments for further validation.

Biography

As a graduate student, Samuel Coulbourn Flores built the HingeMaster and Conformation Explorer hinge and motion prediciton servers, hosted on MolMovDB.org. He developed MMB, the code used in this work, as a Distinguished Fellow in Russ Altman's lab at Stanford. He is now a professor at Uppsala University, Sweden, working on ribosomal mechanics, antibody design, viral genome packaging, and other applications of internal coordinate mechanics.

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