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| **Title** | **Accommodation of aminoacyl-tRNA into the ribosome involves reversible excursions along multiple pathways** |
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| **Publication** | *RNA 2010. 16: 1196-1204* |
| **Abstract** | The ribosome is a massive ribonucleoprotein complex (~2.4 MDa) that utilizes large-scale structural fluctuations to produce unidirectional protein synthesis. Accommodation is a key conformational change during transfer RNA (tRNA) selection that allows movement of tRNA into the ribosome. Here, we address the structure–function relationship that governs accommodation using all-atom molecular simulations and single-molecule fluorescence resonance energy transfer (smFRET). Simulations that employ an all-atom, structure-based (Gō-like) model illuminate the interplay between configurational entropy and effective enthalpy during the accommodation process. This delicate balance leads to spontaneous reversible accommodation attempts, which are corroborated by smFRET measurements. The dynamics about the endpoints of accommodation (the A/T and A/A conformations) obtained from structure-based simulations are validated by multiple 100–200 ns explicit-solvent simulations (3.2 million atoms for a cumulative 1.4 μs), and previous crystallographic analysis. We find that the configurational entropy of the 3′-CCA end of aminoacyl-tRNA resists accommodation, leading to a multistep accommodation process that encompasses a distribution of parallel pathways. The calculated mechanism is robust across simulation methods and protocols, suggesting that the structure of the accommodation corridor imposes stringent limitations on the accessible pathways. The identified mechanism and observed parallel pathways establish an atomistic framework for interpreting a large body of biochemical data and demonstrate that conformational changes during translation occur through a stochastic trial-and-error process, rather than in concerted lock-step motions. |
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