

Register Shifts in Uracil-Damaged DNA

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Why Study Register Shifts?

- To remove uracil (U), a highly mutagenic and common lesion of DNA¹, uracil-DNA glycosylase (UDG) initiates spontaneous uracil flipping to repair².
- It was recently shown that uracil flipping can be accompanied by a register shift, which sterically blocks uracil from re-entry⁴.
- By exposing the lesion longer, register shifting is thought to be important for DNA repair, hotspot genesis, and molecular evolution⁴.

Procedure

Input System

a) U:A Base Paired Sequences

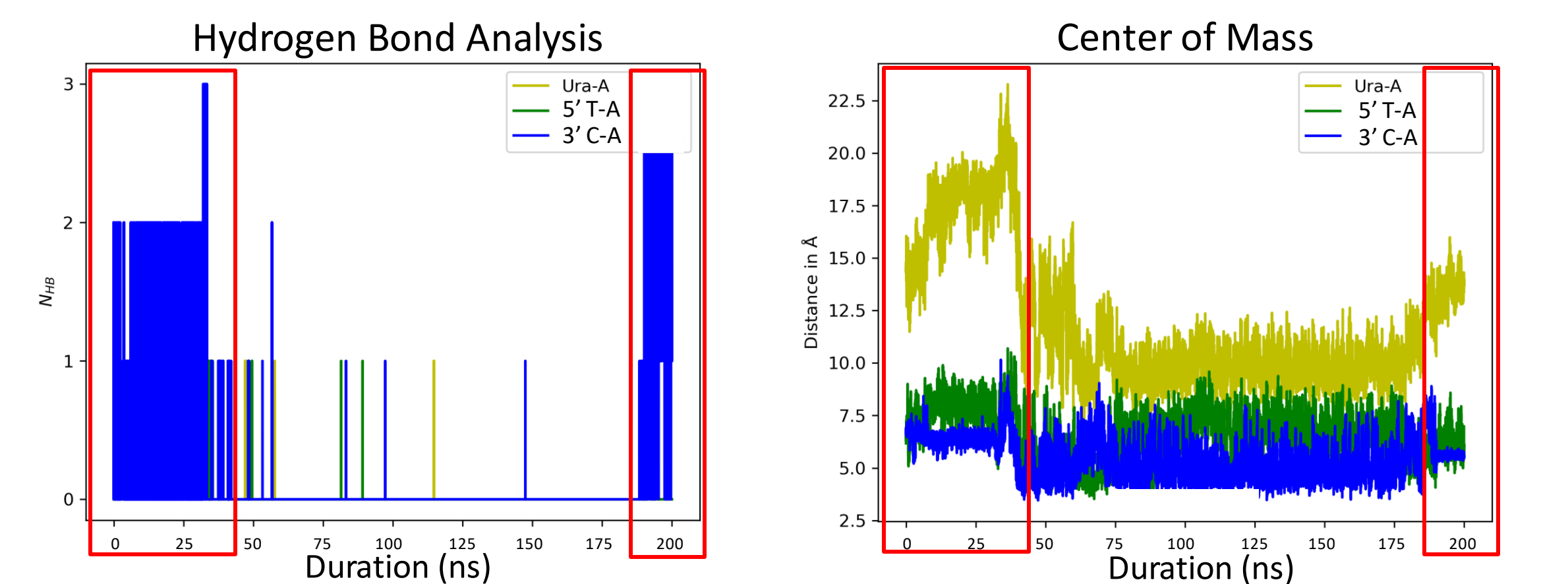
XTUY motif:
3' – GCGC xAAy GCGC – 5'
5' – CGCG XT UY CGCG – 3'

b) U:G Base Paired Sequences

XTUY motif:
3' – GCGC xAGy GCGC – 5'
5' – CGCG XT UY CGCG – 3'

MD Simulations

- U flipping to both major and minor grooves was considered. Out of the 32 total sequences simulated, three sequences displayed persistent register shifts and were further analyzed.



Results

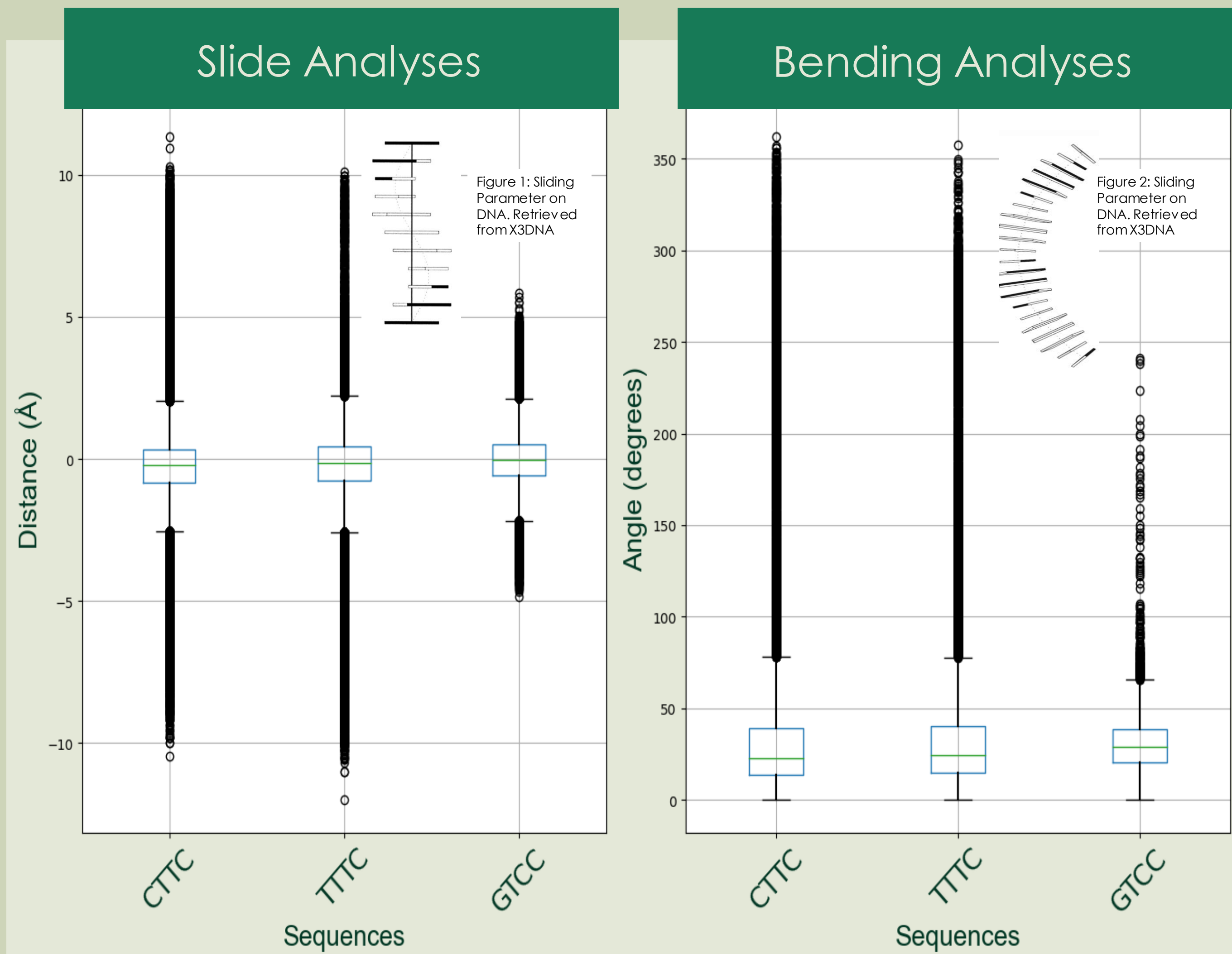


Table 1. Register Shifts In U:G Base Paired XTUY Sequences

Sequence	Duration (ns)
GTUC-Major	50.33

Table 2. Register Shifts In U:A Base Paired XTUY Sequences

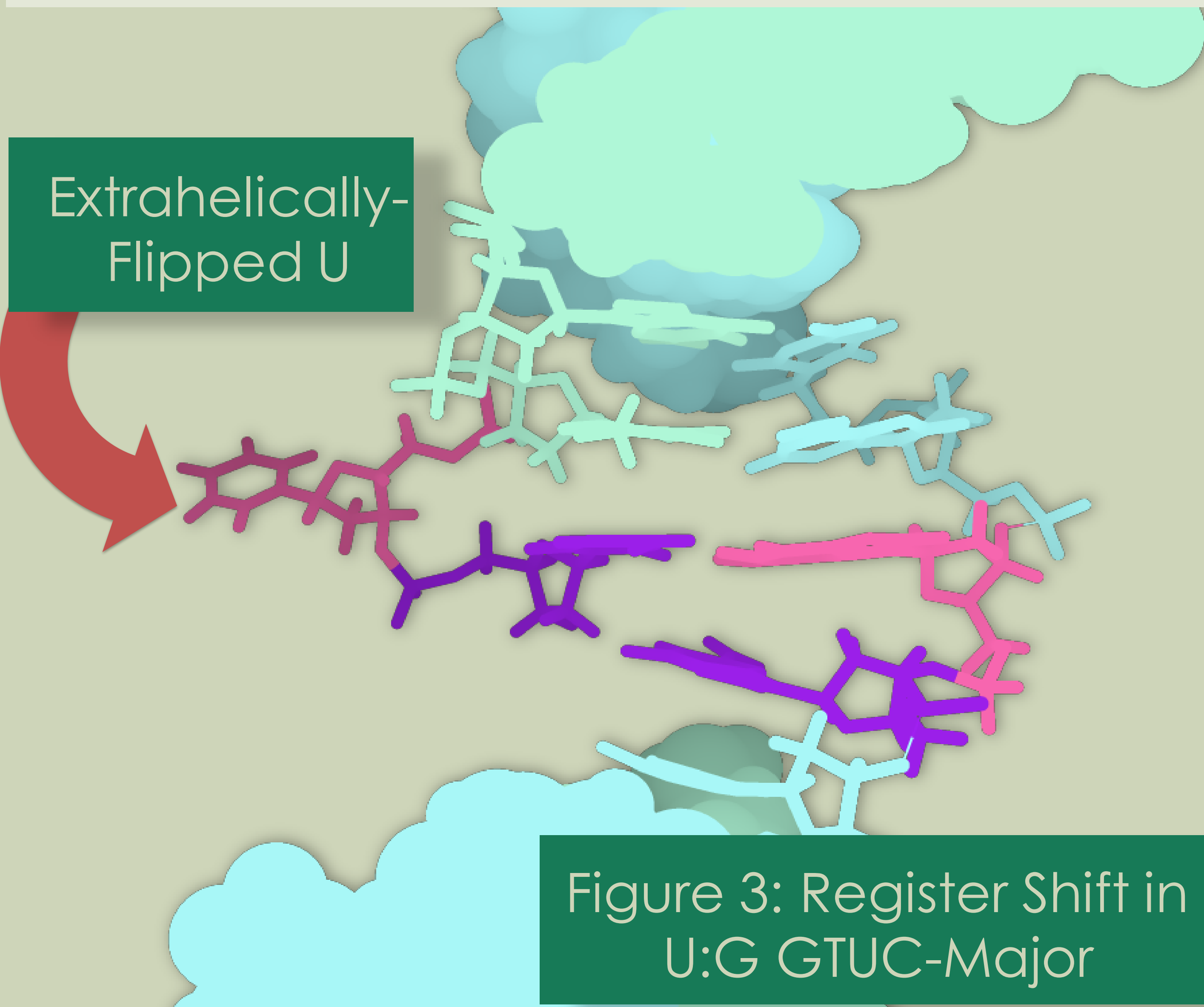
Sequence	Durations (ns)
TTUC-Major	9.78, 33.19
CTUC-Major	.02, 3.42

Trends Discovered

- RS occur most for **3' cytosines** on the U strand.
- Duration for RS was **longest in U:G base paired XTUY sequences**.
- Preference of register shifting for **major groove** for both U:A and U:G base paired strands.

Further Works

- Extend simulations for sequences that continue to have U flipped out.
- Conduct further statistical analyses on other base parameters.



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