Supplementary Materials

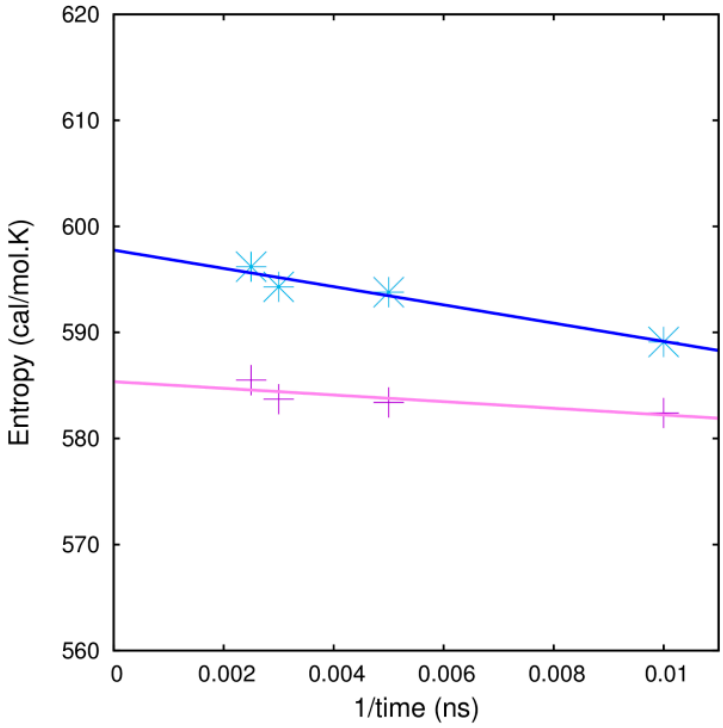

Figure S1. Entropy contributions calculated over time windows 100–200 ns, 100–300 ns, 100–400 ns, and 100–500 ns for the wild-type (wt) (purple crosses) and UII_CII_AII systems (blue asterisks).

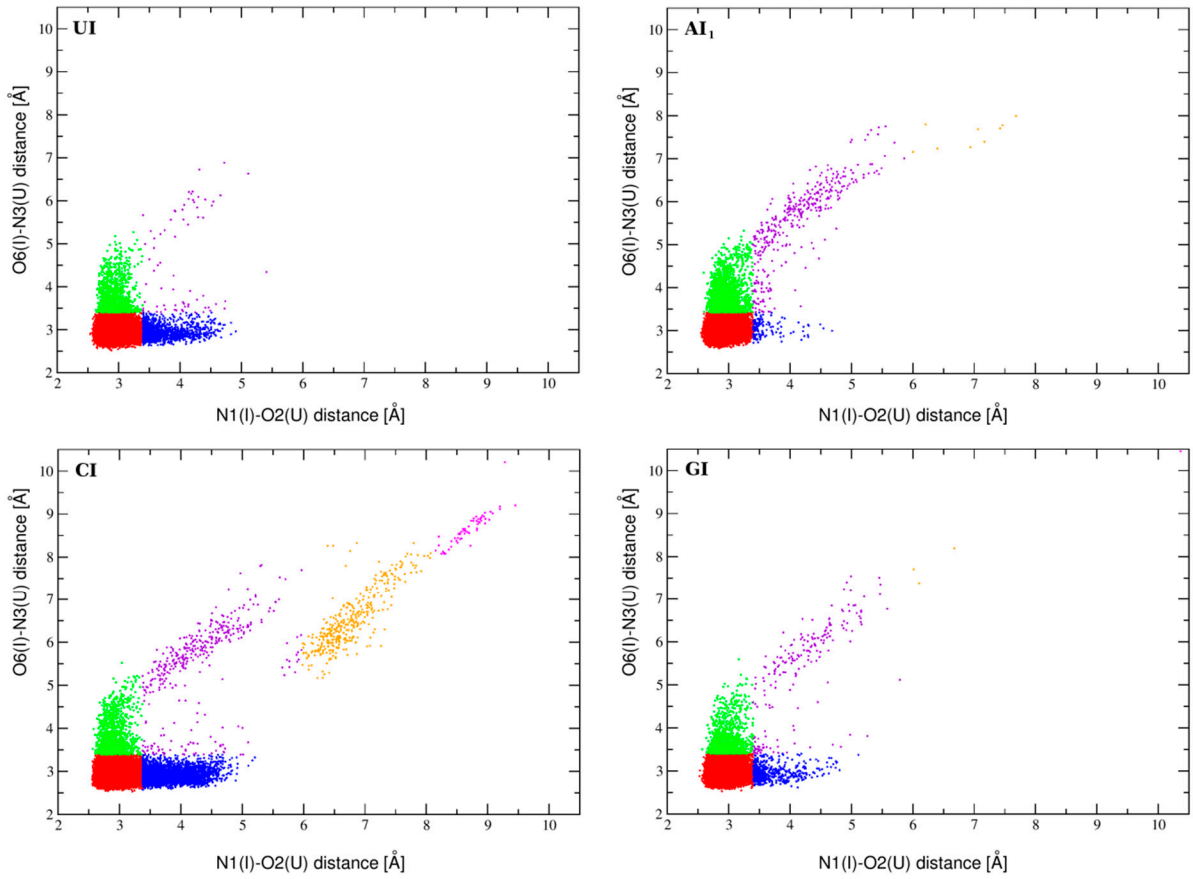

Figure S2. Distribution of various geometries of the inosine–uracil (I–U) base pair observed in the single I–U systems as a result of correlation between N1(I)–O2(U) and O6(I)–N3(U) H-bond distances. The AI_1 system was selected as a representative of the AI sequence motif. The initial geometry (in red) is predominantly populated (above 90%), while populations of B (in blue) and C (in green) geometries are ca. 1-5%, and D, E, and F geometries (in violet, orange, and magenta) do not exceed 1%. Colors of substates correspond to Figure 4 in the main text.

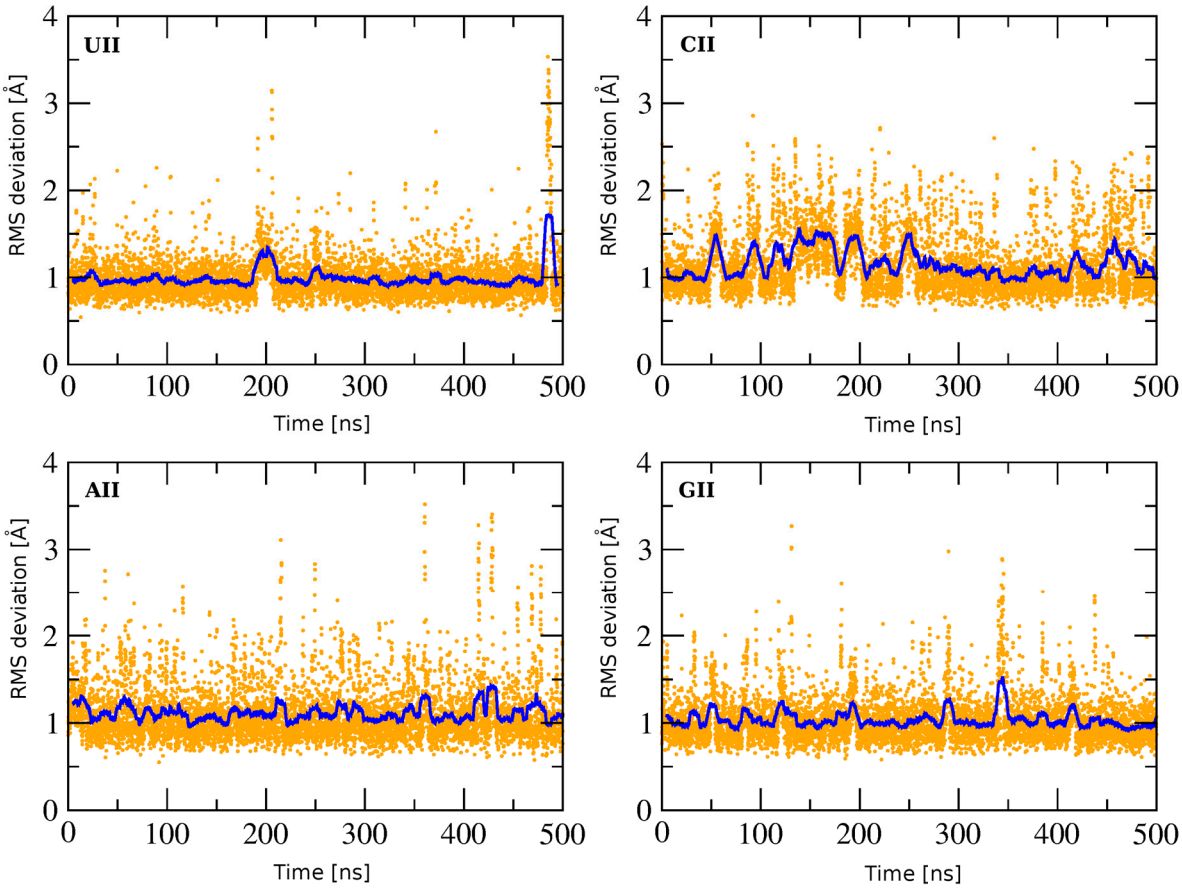

Figure S3. Root mean square (RMS) deviations along the production trajectories evaluated for the tandem I–U/I–U systems. RMSd was calculated for the I–U/I–U core supplemented by 5′ and 3′ base pair neighbors. The minimized structure with corrected I–U geometry was used as a reference.

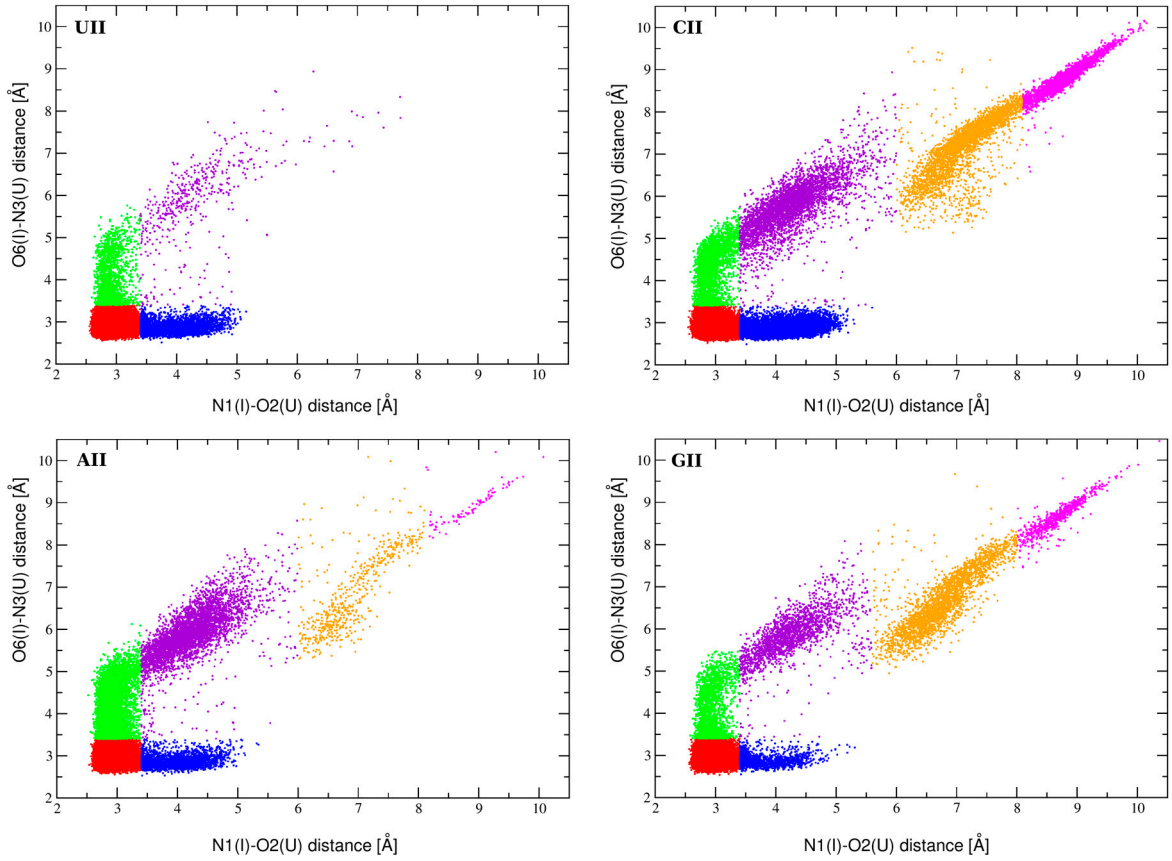

Figure S4. Distribution of various geometries of the first I–U base pair observed in the I–U/I–U tandem systems as a result of correlation between N1(I)–O2(U) and O6(I)–N3(U) H-bond distances. Substate populations are roughly distinguished by different colors, which corresponds to Figure 4 in the main text.

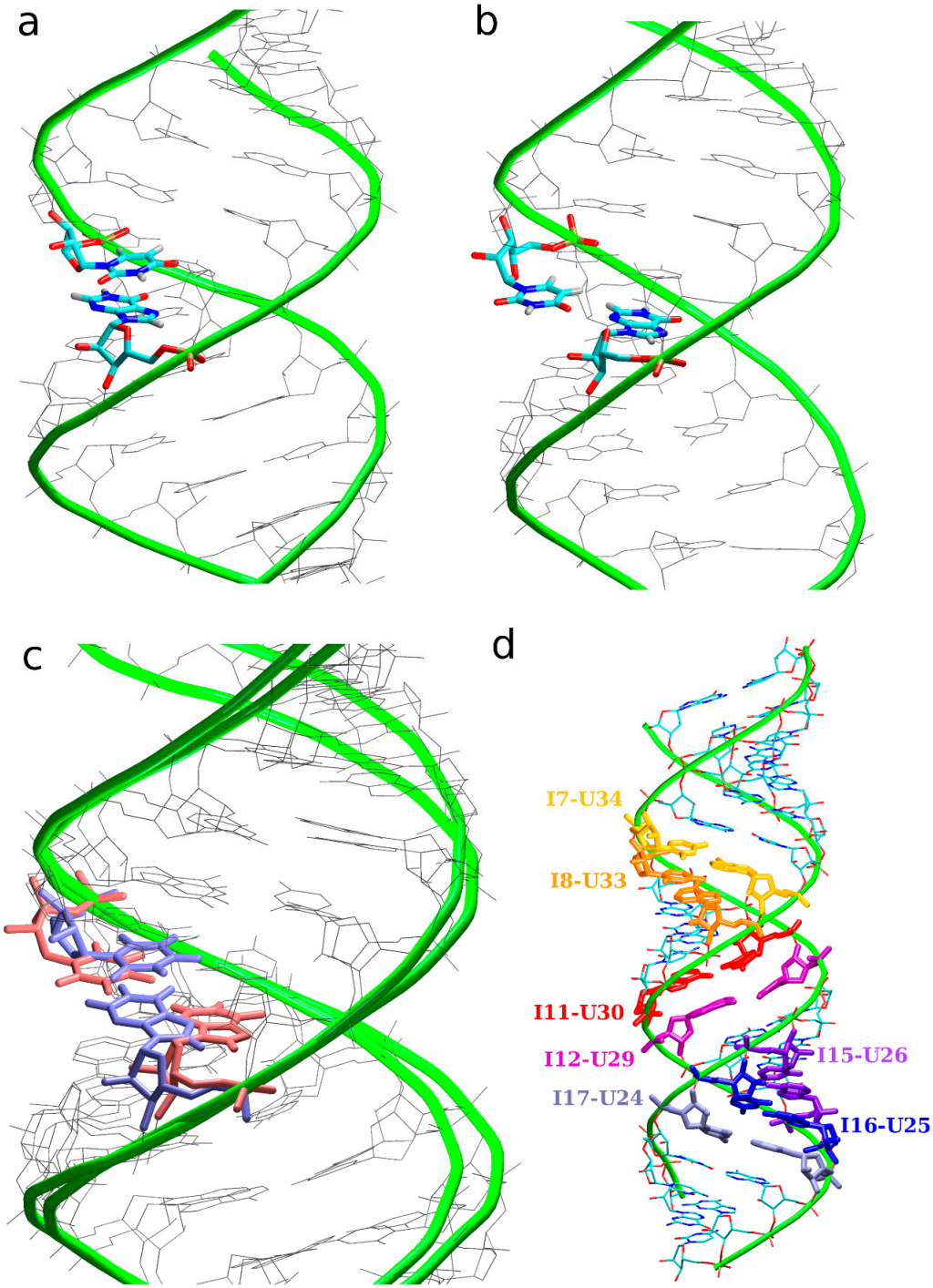

Figure S5. Selected structures from molecular dynamics (MD) simulations. (**a**) A snapshot of the UII system in the A-geometry (I7–U34 base pair is highlighted); (**b**) a snapshot of the CII system in the F-geometry (I11–U30 base pair is highlighted); (**c**) an overlay of A- and F-geometries in the CII system (the A-geometry in violet, the F-geometry in pink); and (**d**) distribution of I–U base pairs along the RNA duplex.

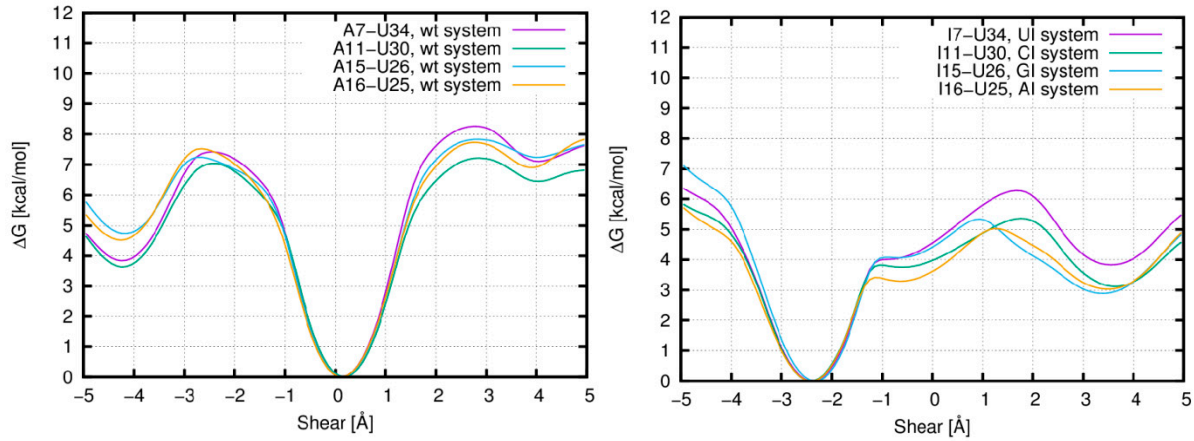

Figure S6. Free energy profiles of A–U and single I–U pairs based on adaptive biasing method (ABF) simulations.

Table S1. Two-term coefficients describing editing frequencies by adenosine deaminases acting on RNA (ADAR)1 and ADAR2 based on experimental study[1].

base	coefficients for the first 5′ neighboring base (ADAR1)	coefficients for the first 3′ neighboring base (ADAR1)	coefficients for the first 5′ neighboring base (ADAR2)	coefficients for the first 3′ neighboring base (ADAR2)
A	0.86	1.48	1.17	0.87
C	0.25	1.56	0.43	1.45
G	0.046	1.94	0.052	1.9
U	1.75	1	1.69	1

[1]Eggington et al., *Nat. Commun.* **2011**, *2*, 319, 10.1038/Ncomms1324

Table S2. Averaged local bend values calculated for twelve selected systems

step	wt	UII	CII	GII	AII	UI	AI_1	CI	AI_2	GI	AI_3	AI_4
1	6.7	6.7	6.9	6.8	6.8	6.8	6.7	6.8	6.8	6.7	6.8	6.8
2	14.4	15	14.9	14.7	14.6	15	14.5	14.8	14.7	14.7	14.6	14.8
3	11.7	12.8	11.8	11.7	11.6	12.3	12.1	11.8	11.8	12	11.7	11.8
4	9.7	11	9.6	9.5	9.5	10.1	10.3	9.4	9.6	9.8	9.6	9.6
5	11.5	11.5	11.2	11.3	11.3	10.7	11.7	11.1	11.1	11.4	11.2	11.4
6	14.7	15.8	14.5	14.7	14.5	15.5	15.2	14.3	14.2	14.5	14.5	14.7
7	9.5	**12.2**	10.1	9.5	9.4	9.8	11.4	9.9	9.5	9.5	9.4	9.4
8	7.7	7.6	8.1	7.6	7.6	7.7	7.9	7.9	7.7	7.6	7.6	7.6
9	10	11	9.4	9.9	10	9.5	11.8	9	10	10	10	10
10	11.9	11.9	10.6	11.7	11.8	11.2	12.7	11.4	10.9	11.9	11.8	11.8
11	8.6	8.3	**11.4**	9.1	8.5	8.8	8.4	8.7	**11.2**	8.9	8.6	8.5
12	9	9	8.2	9.8	9.5	9.2	8.9	9.1	8.5	9.4	9.5	9.1
13	10.4	10.3	10.3	10.7	11.2	10.4	10.2	9.7	10.8	10.4	11	10.7
14	10.7	10.8	10.4	11.2	9.7	10.6	10.7	10.5	10.5	11.7	9.9	11.1
15	10.7	10.8	10.5	**12.9**	11.4	10.6	10.7	10.7	10.6	11.6	12.1	10.1
16	11.3	11.3	11.3	12.9	**13.8**	11.1	11.1	11.3	11.1	12.2	11.9	13.2
17	10.4	10.3	10.6	11	10.9	10.2	10.3	10.3	10.6	9.7	11.1	10.3
18	10.3	10.3	10.5	9.6	11.3	10.5	10.4	10.3	10.4	10	9.9	12.3
19	6.5	6.5	6.5	6.5	6.2	6.5	6.6	6.5	6.5	6.6	6.4	6.2

Values larger than 2 Å when compared with the wt system are in bold.