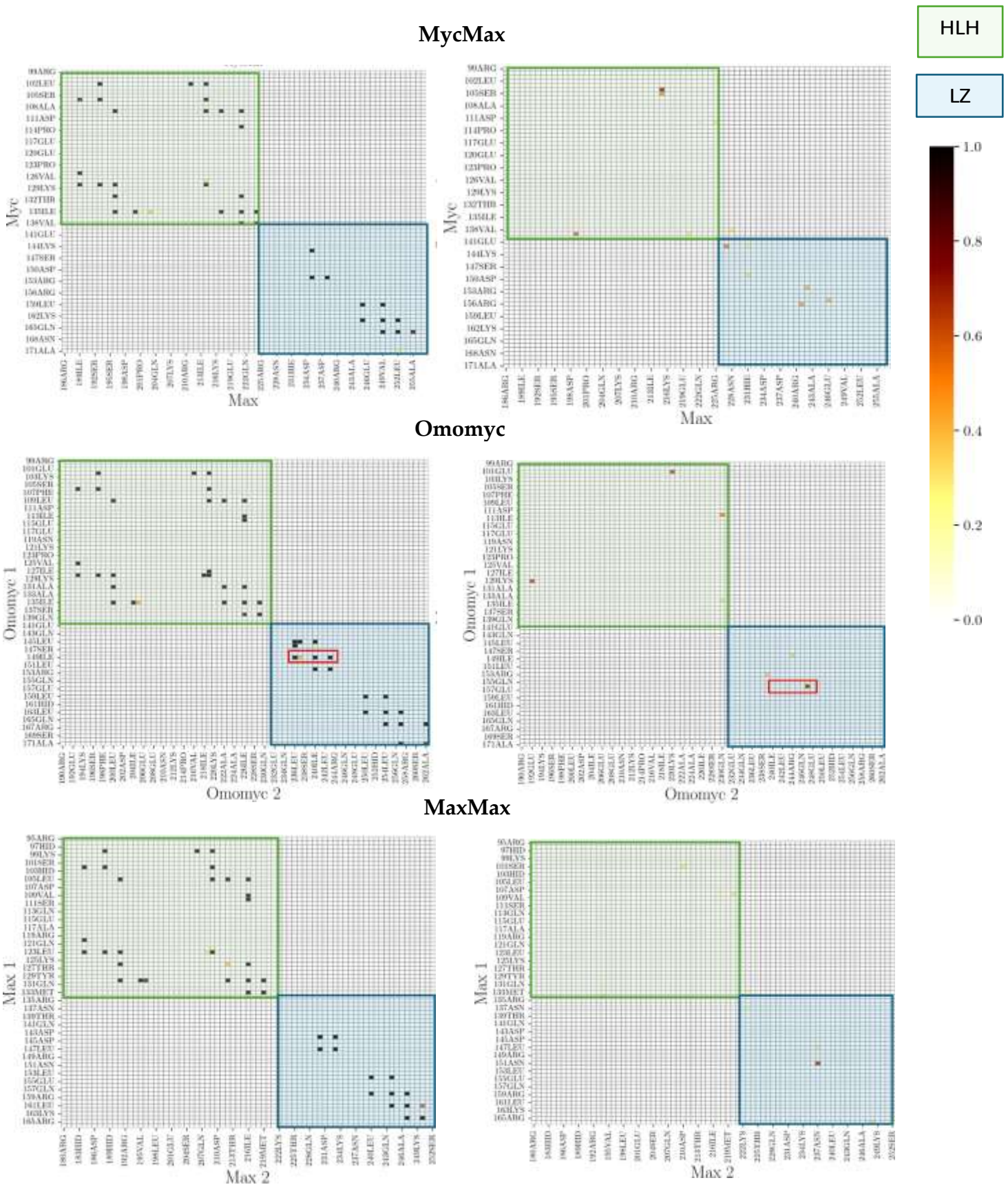


Figure S1: Hydrophobic Interactions and Hydrogen Bonds (HBs) in the HLH and LZ regions of MycMax, Omomyc dimer, and MaxMax. Left panels show a heatmap of the hydrophobic contacts (a contact is recorded when the distance between two hydrophobic residues is within 4.5 Å). Right panel shows a heatmap of the HBs. HLH region is highlighted in green, LZ region in blue. The contacts that were introduced due to the mutation of the 4 residues in Omomyc are highlighted by the red box.

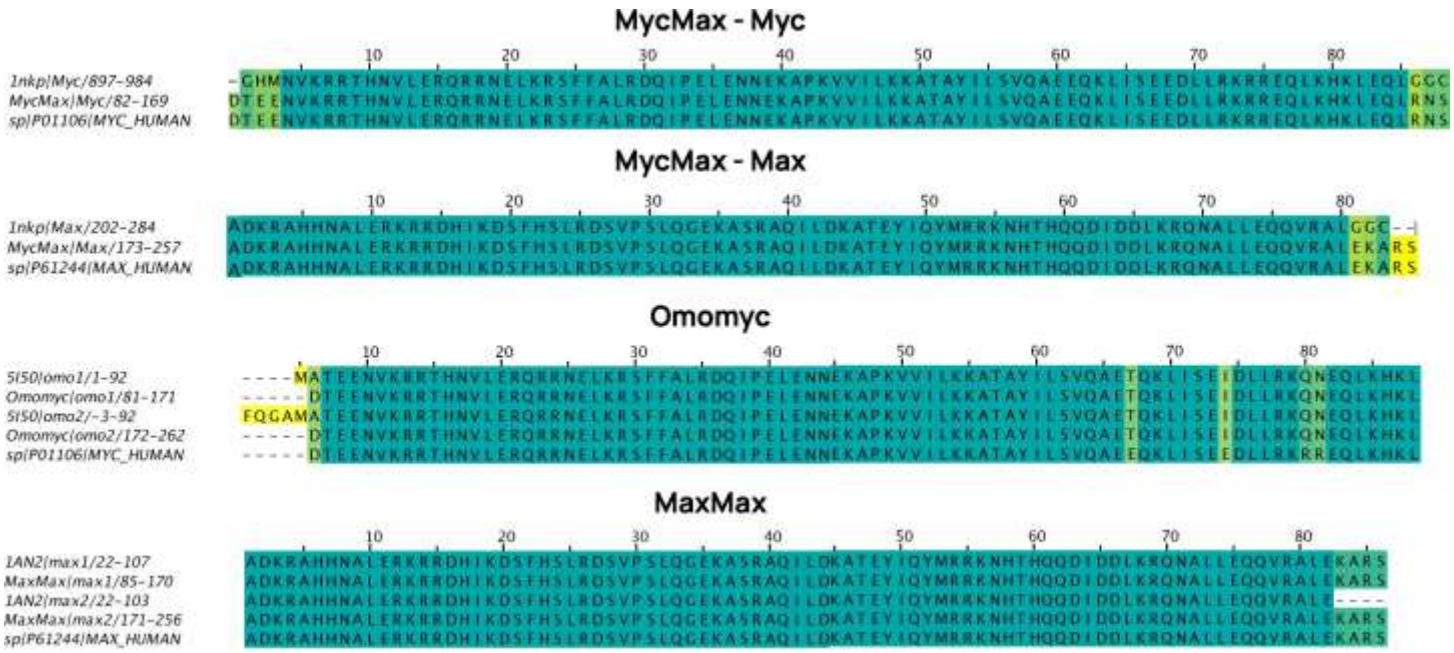


Figure S2: Sequence alignment between the original PDB structures (1NKP for MycMax, 5I50 for Omomyc, and 1AN2 for MaxMax), the processed structures used in this study (MycMax, Omomyc, MaxMax), and the UniProt reference sequences (P01106 for Myc and Omomyc, P61244 for Max). The alignment compares individual monomers from the PDB (1NKP/Myc, 1NKP/Max, 5I50/Omo1, 5I50/Omo2, 1AN2/Max1, and 1AN2/Max2) with their corresponding processed structures (MycMax/Myc, MycMax/Max, Omomyc/Omo1, Omomyc/Omo2, MaxMax/Max1, and MaxMax/Max2) and the reference uniprot sequence (sp/P01106 for Myc and Omomyc, sp/P61244 for Max).

System:Chain	Start Residue	Start Residue in PDB	Start Residue in UNIPROT
MycMax: Myc	D:81	N:900 (DTEE inserted at 896-899)	D:366
MycMax: Max	A:172	D:202 (A inserted at 201)	A:23
Omomyc: Omo1	D:81	D:2	D:366
Omomyc:Omo2	D:172	D:2	D:366
MaxMax:Max1	A:85	A:22	A:23
MaxMax:Max2	A:171	A:22	A:23

Figure S3: Mapping of residue numbering between our processed systems (Start Residue), the original PDB structures (Start Residue in PDB), and the corresponding UniProt residue (Start Residue in UNIPROT) numbers for each chain. Residues that were added to the PDB are shown in parentheses.

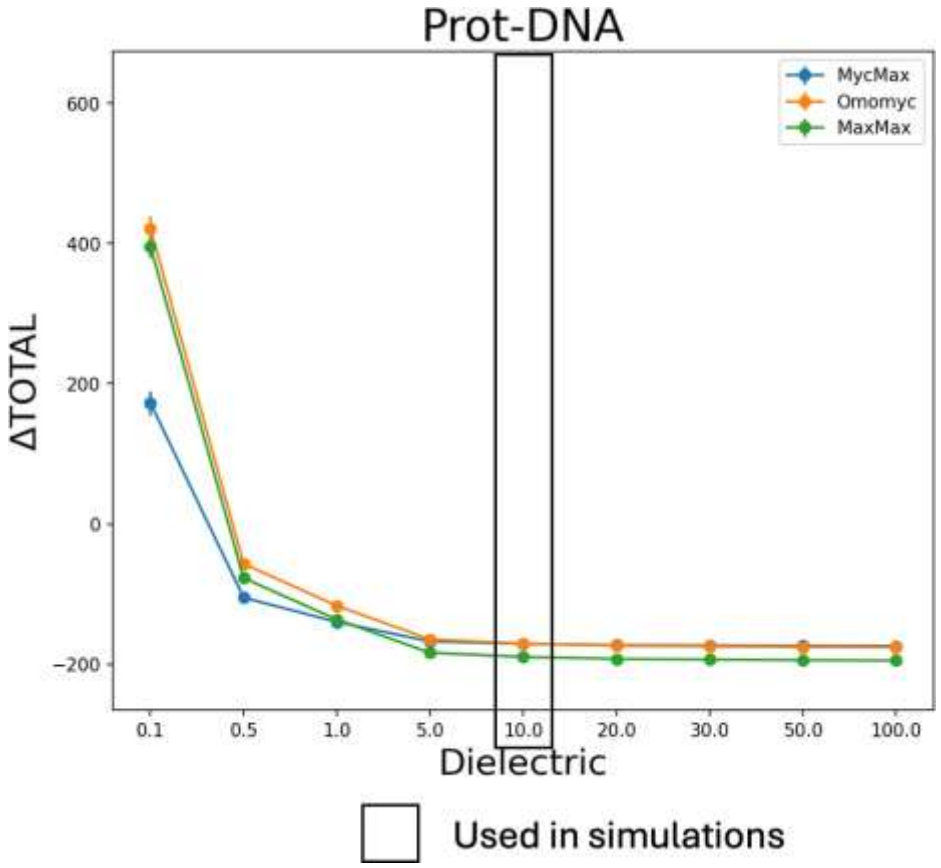


Figure S4: Variation in total MMGBSA binding energy for MycMax (blue), Omomyc (orange), and MaxMax (green) across diZerent dielectric constants. The dielectric constant used in final MMGBSA calculations is highlighted with a box.

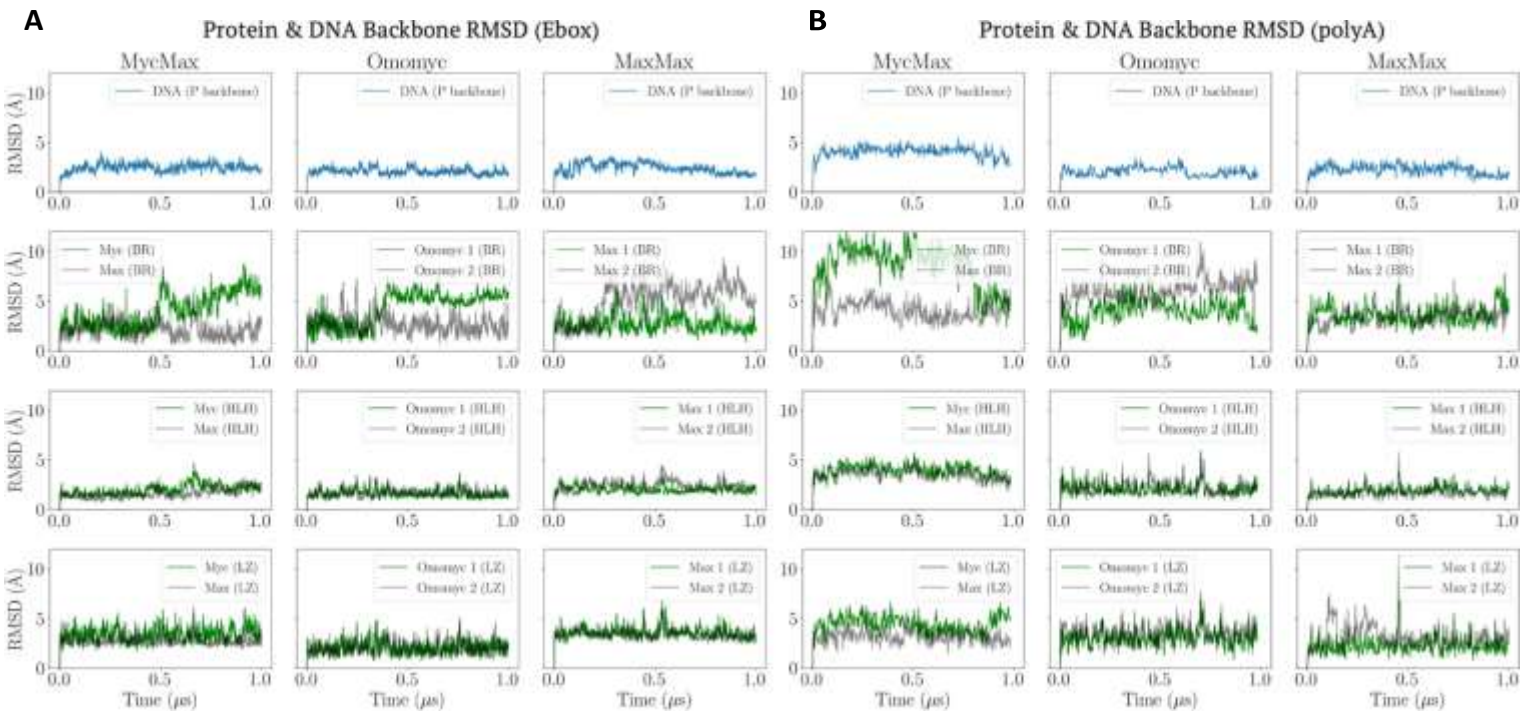


Figure S5: RMSD of protein and DNA backbone for MycMax, Omomyc dimer, and MaxMax complexes bound to E-box (A) and polyA (B). First row is the RMSD of the P atoms of the DNA, second, third and fourth rows are the RMSDs of the heavy atoms of the BR, HLH, and LZ regions for each monomer.

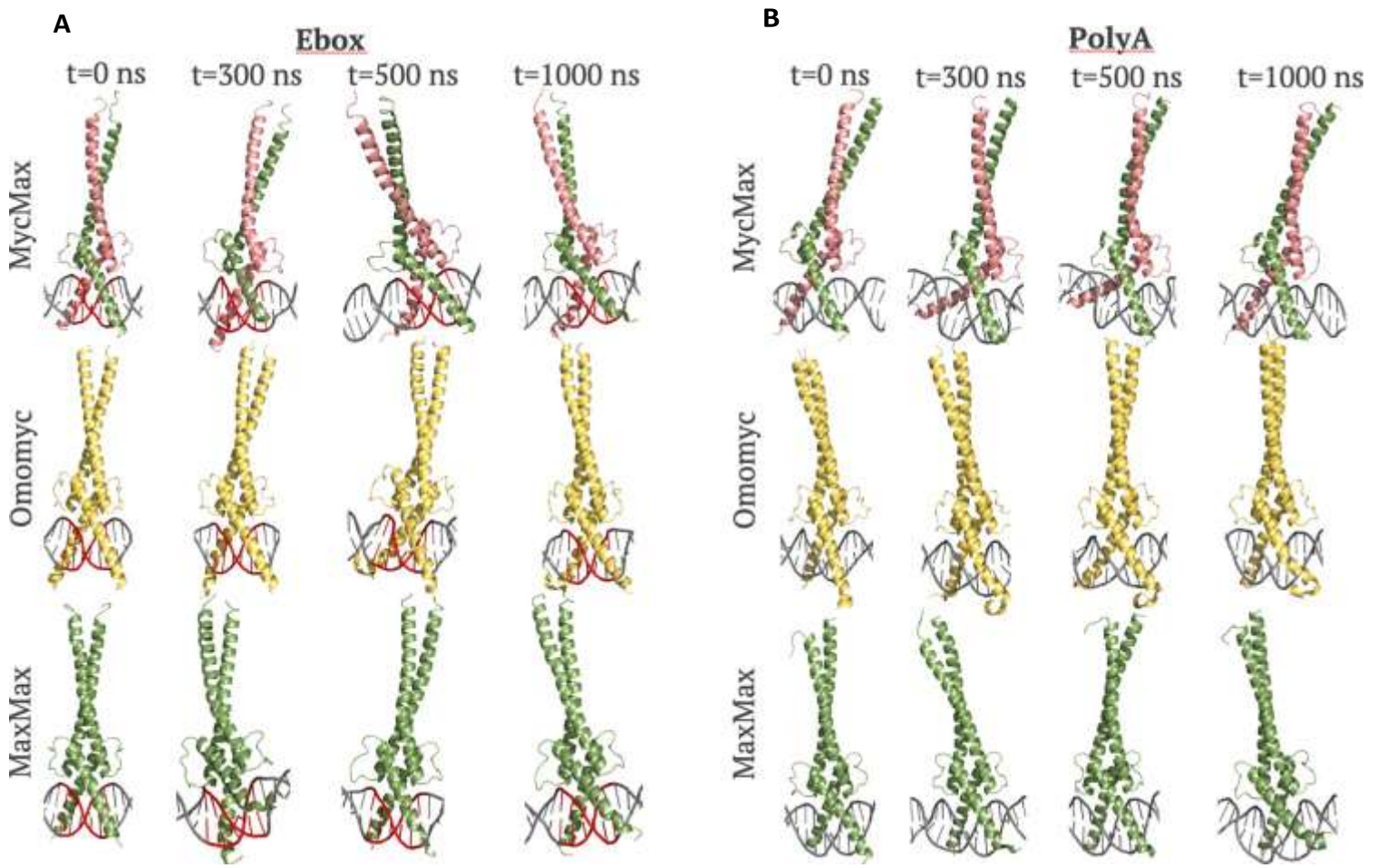
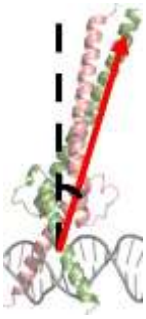


Figure S6. Structural snapshots of MycMax, Omomyc dimer, and MaxMax bound to E-box (A) or polyA (B) at diZerent simulation times (t = 0 ns, 300 ns, 500 ns, 1000 ns). Myc is shown in pink, Max in green, and Omomyc in yellow, with the E-box highlighted in red. Panel (A), previously shown in Figure 2A, is included here for direct comparison with (B), illustrating structural diZerences in TF binding between E-box (A) and polyA (B).



Angle Deviation (°)	MycMax	Omomyc	MaxMax
Ebox	16 ± 9	11 ± 6	12 ± 5
PolyA	14 ± 3	7 ± 4	5 ± 3

Figure S7: Angular deviation of the HLHLZ domain measured from the simulation. The average and standard deviation of the angle (as shown in the diagram on the left) were measured for MycMax, Omomyc dimer and MaxMax on Ebox and PolyA across the 1-microsecond trajectory.

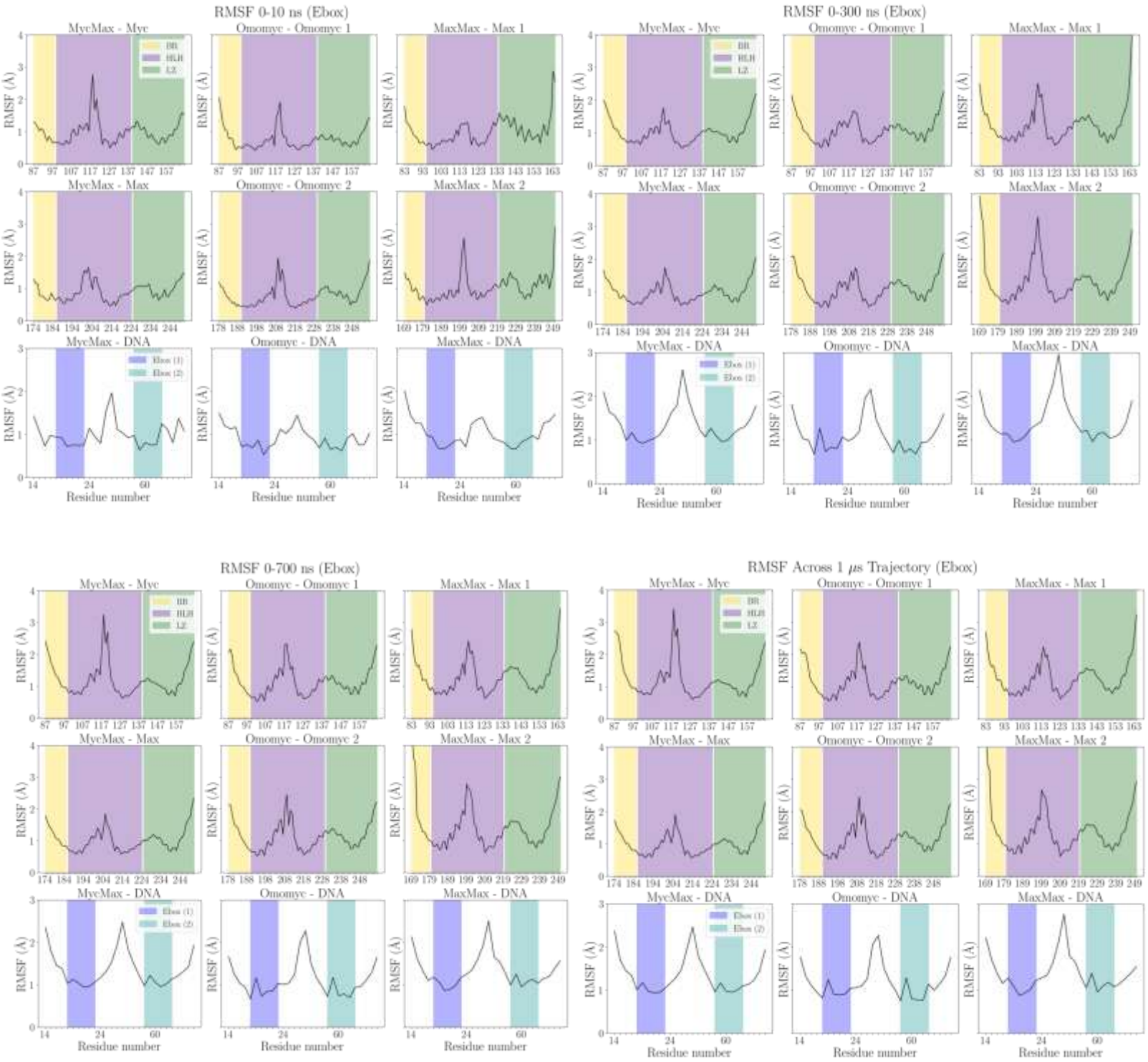


Figure S8: RMSF plots for MycMax, Omomyc dimer, and MaxMax complexes bound to Ebox. RMSF is measured for each monomer (top two rows), as well as for both DNA strands (bottom row, strands delimited by dashed lines), over 10ns (top left), 300ns (top right), 700ns (bottom left), and 1000ns (bottom right) of simulation time. The protein regions are color-coded: BR (yellow), HLH (purple), LZ (green), and the E-box on each DNA strand (blue).

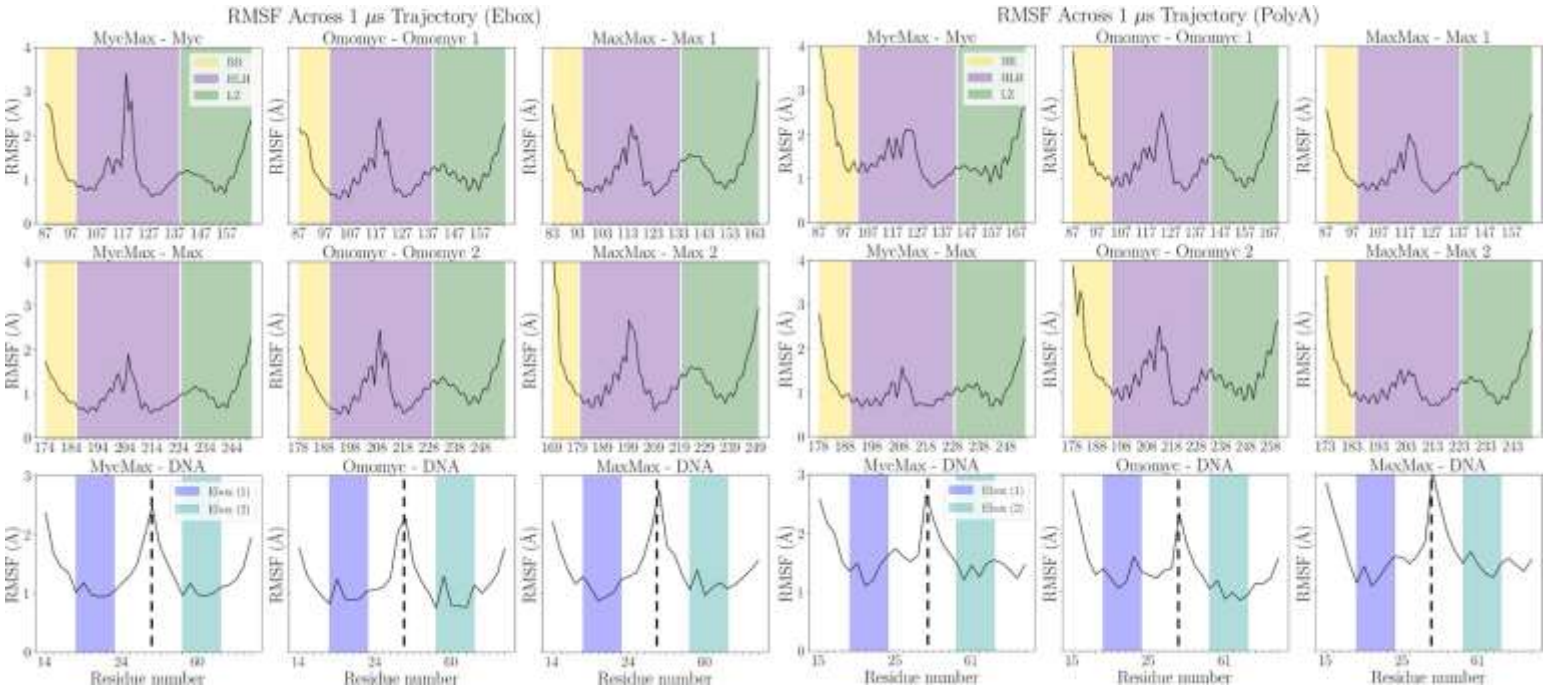


Figure S9: RMSF plots for MycMax, Omomyc dimer, and MaxMax complexes bound to Ebox (left) and polyA (right) over 1000ns of simulation time. RMSF is measured for each monomer (top two rows), as well as for both DNA strands (bottom row, strands delimited by dashed lines. The protein regions are color-coded: BR (yellow), HLH (purple), LZ (green), and the central region for polyA on each DNA strand (blue).

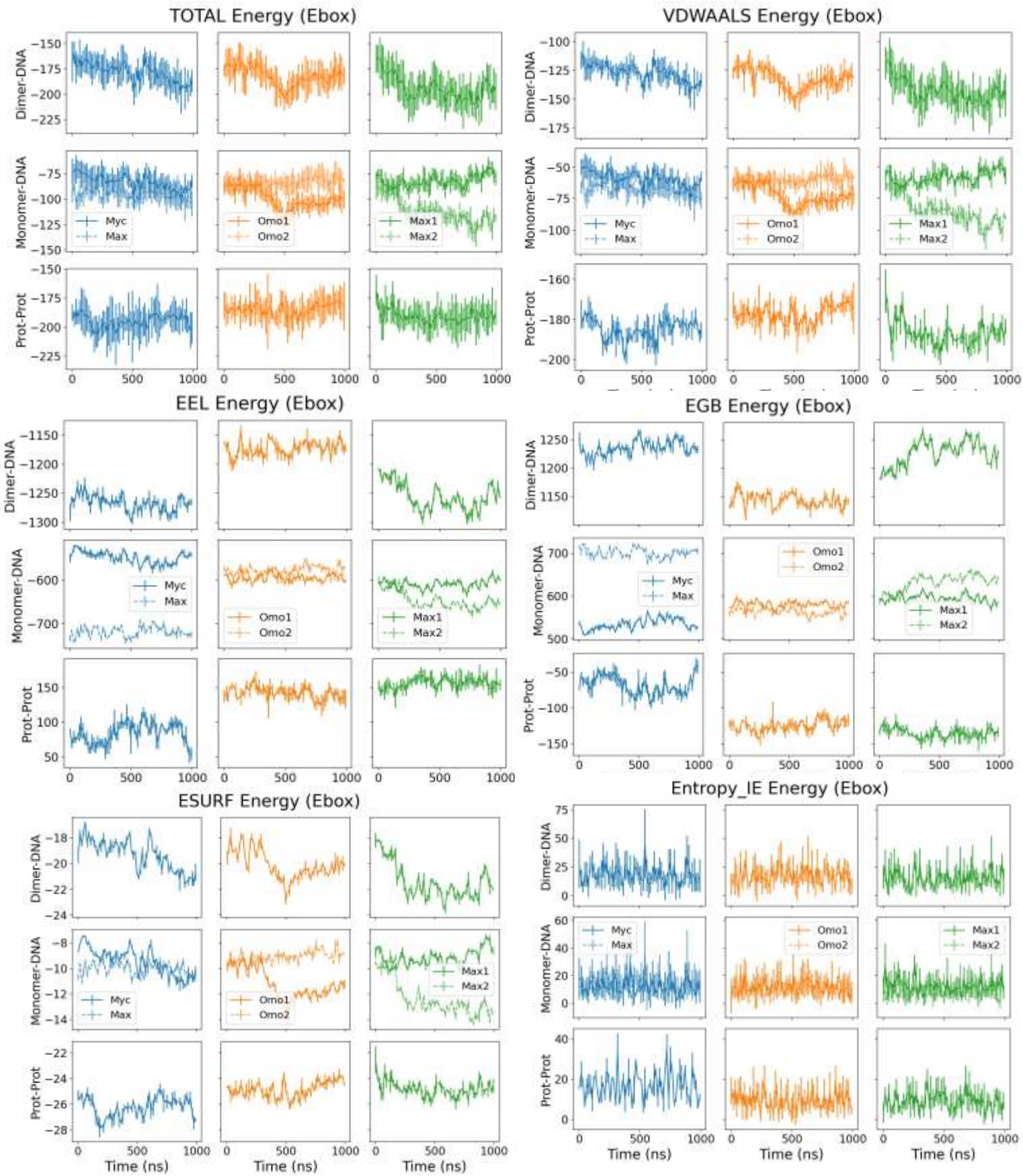


Figure S10: Energy Decomposition over Time for MycMax (blue), Omomyc dimer (orange), and MaxMax (green) Complexes bound to E-box. Time series plots are shown of various regions (entire system in the first row, each monomer interaction with DNA in the second row, and monomer-monomer interactions in the third row) over a 1 μs simulation period. The energy components include TOTAL (Total binding energy), VDWAALS (van der Waals interactions), EEL (Electrostatic energy), EGB (Polar solvation energy), ESURF (non-polar solvation energy) and IE (interaction entropy).

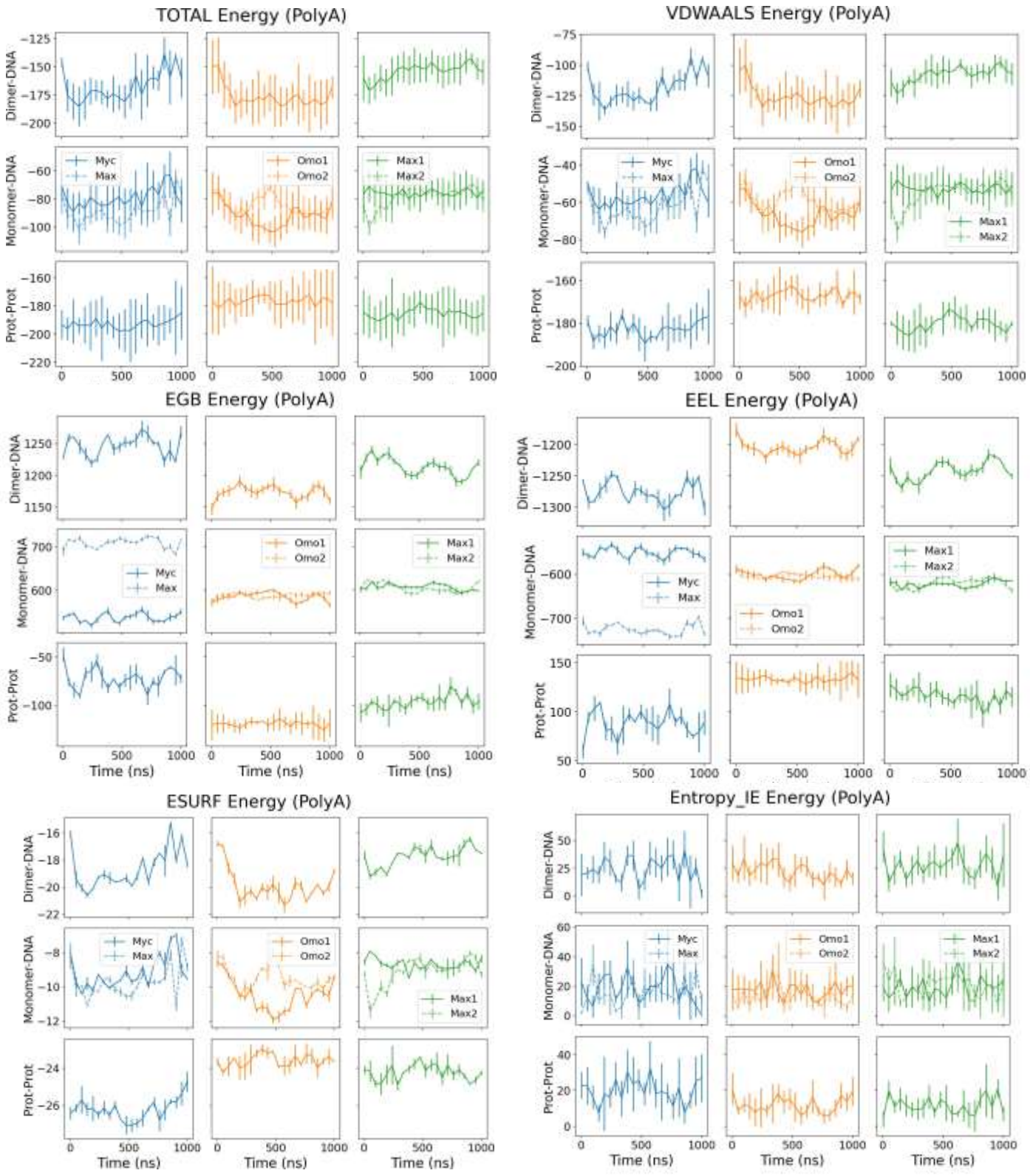


Figure S11: Energy Decomposition over Time for MycMax (blue), Omomyc dimer (orange), and MaxMax (green) Complexes bound to PolyA. Time series plots are shown of various regions (entire system in the first row, each monomer interaction with DNA in the second row, and monomer-monomer interactions in the third row) over a 1 μs simulation period. The energy components include TOTAL (Total binding energy), VDWAALS (van der Waals interactions), EEL (Electrostatic energy), EGB (Polar solvation energy), ESURF (non-polar solvation energy) and IE (interaction entropy).

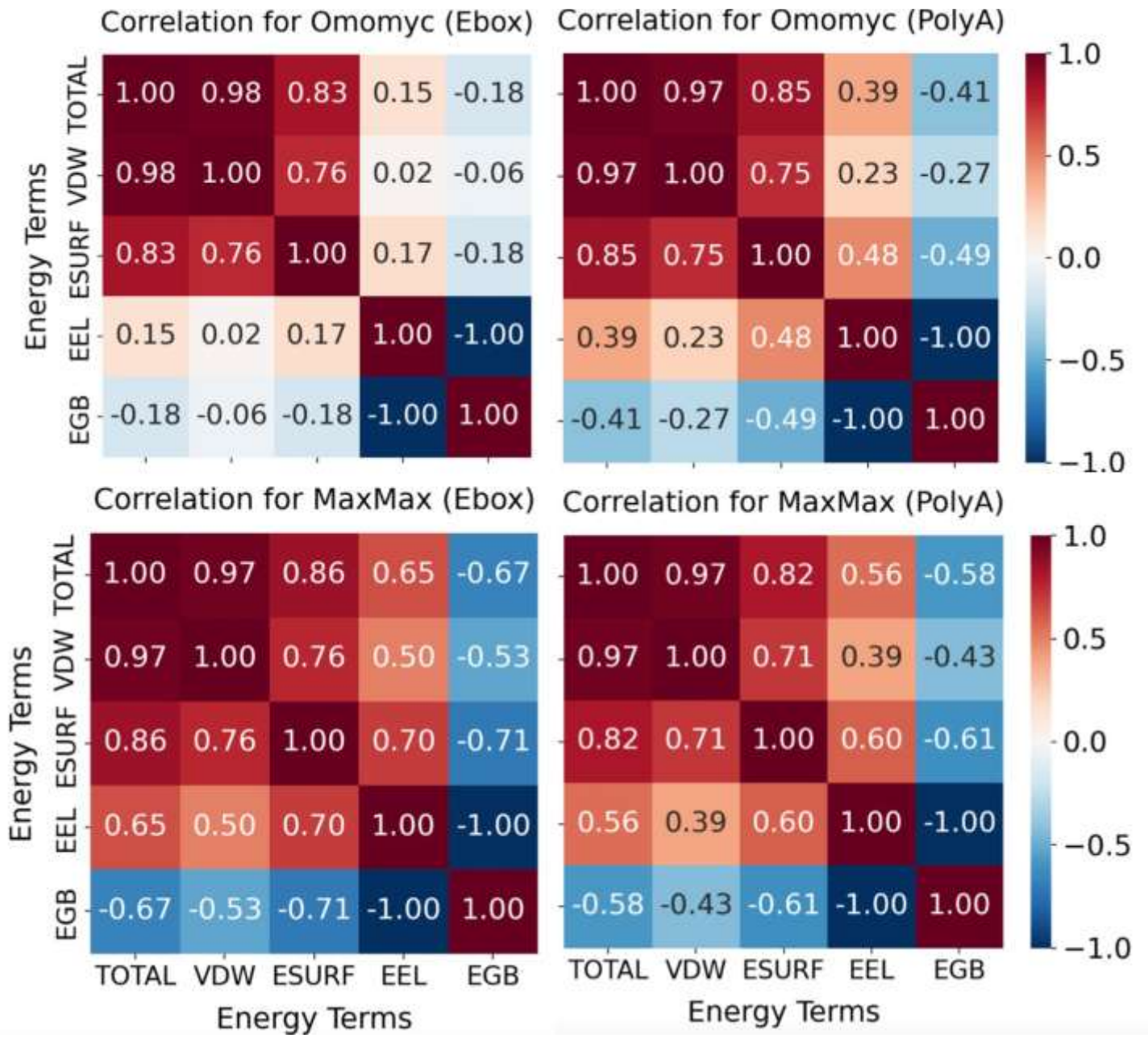


Figure S12: Pearson correlation coeZicient between energy terms TOTAL (Total binding energy), VDW (van der Waals interactions), EEL (Electrostatic energy), EGB (Polar solvation energy), ESURF (non-polar solvation energy) for Ebox (left) and polyA (right) systems. Omomyc terms are shown on the first row, MaxMax on the second.

A

System	-TΔS (kT)
MycMax	12 (7)
Omomyc	10 (6)
MaxMax	9 (5)
MycMax (polyA)	9 (9)
Omomyc (polyA)	13 (7)
MaxMax (polyA)	16 (9)

B

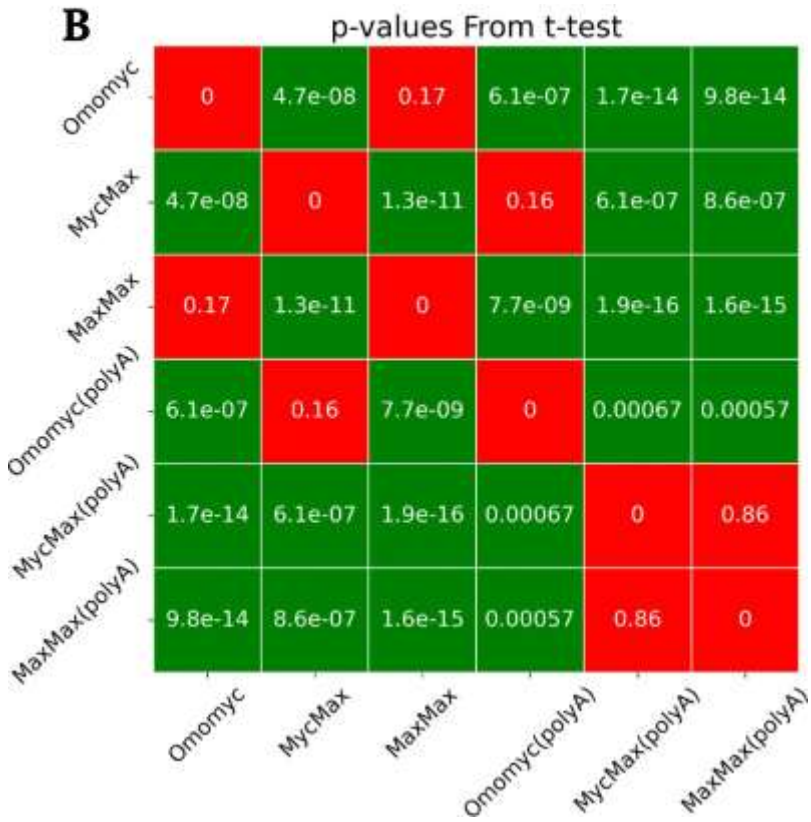


Figure S13. (A) p-values obtained from a two-sample t-test comparing the interaction entropies between pairs of systems. The null hypothesis assumes that the entropic contributions to binding are identical between the two compared systems. A small p-value (<0.05, shown in green) indicates a statistically significant diZerence in entropy between the systems, suggesting distinct entropic contributions, whereas a large p-value (>0.05, shown in red) suggests no significant diZerence. (B) The mean and standard deviation of the entropic contribution to the binding free energy across all systems.

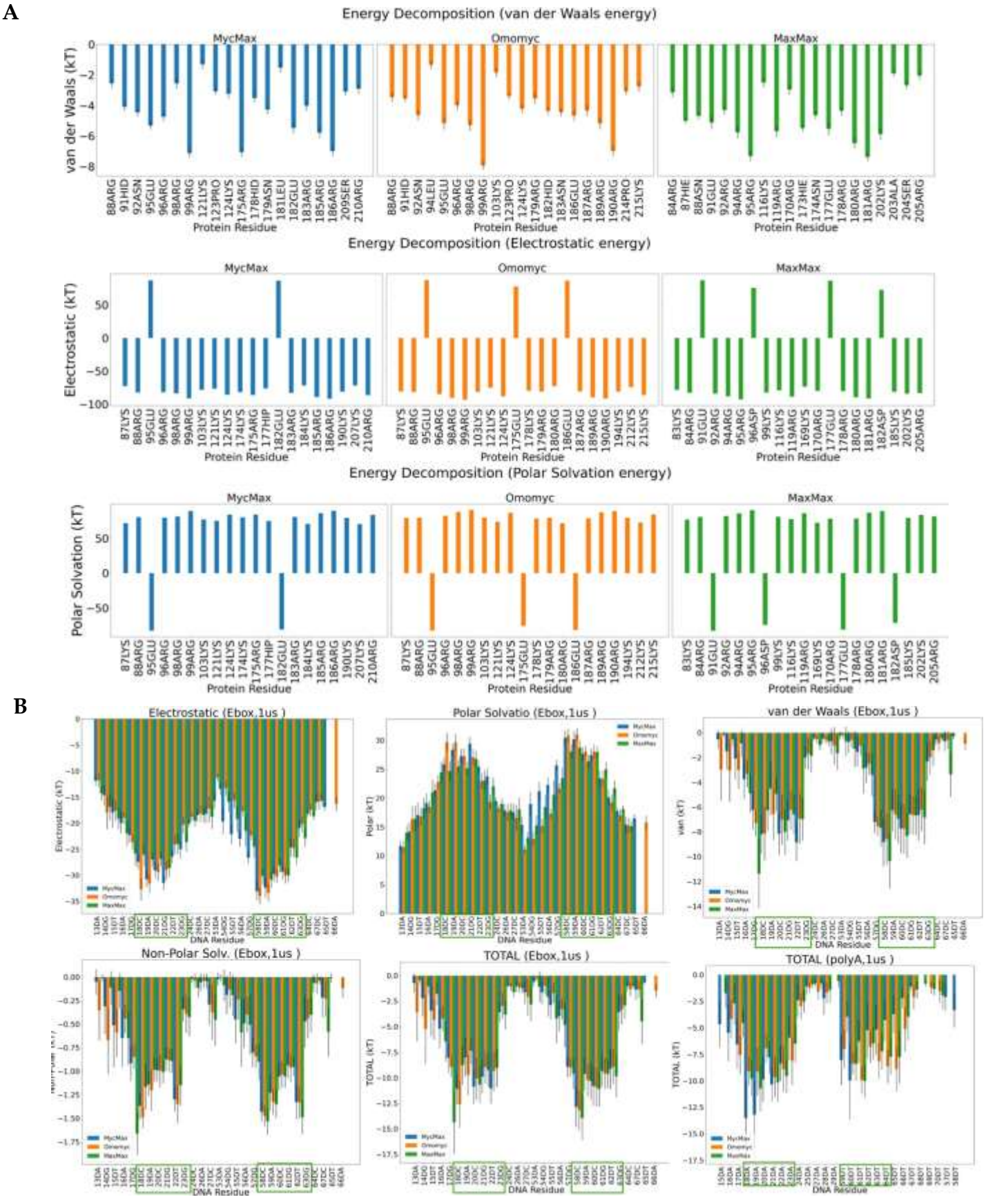
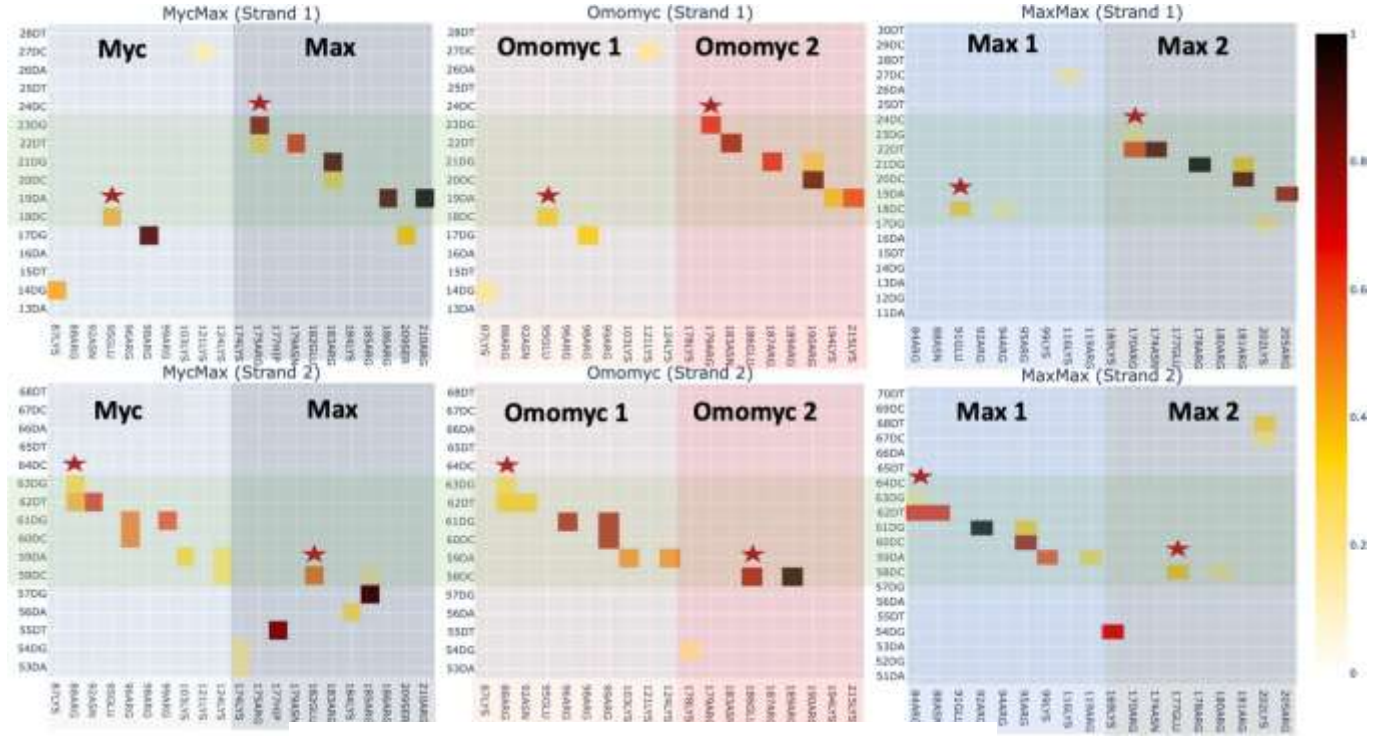


Figure S14: Energy Decomposition Analysis for MycMax, Omomyc dimer, and MaxMax Complexes. (A) Per-residue energy decomposition for protein residues in MycMax, Omomyc, and MaxMax complexes. The plots display the contributions of van der Waals energy, electrostatic energy, and polar solvation energies for the top 20 contributing protein residues. (B) Per-residue energy decomposition for DNA residues in MycMax (blue), Omomyc (orange), and MaxMax (green) complexes bound to polyA (last panel, bottom right) and Ebox. The plots show the contributions of van der Waals, Electrostatic, Polar Solvation, Non-Polar Solvation Energies, and the total energy. The E-box region is highlighted in the green box.

HB Interactions, 0-10 ns



HB Interactions, 0-300 ns

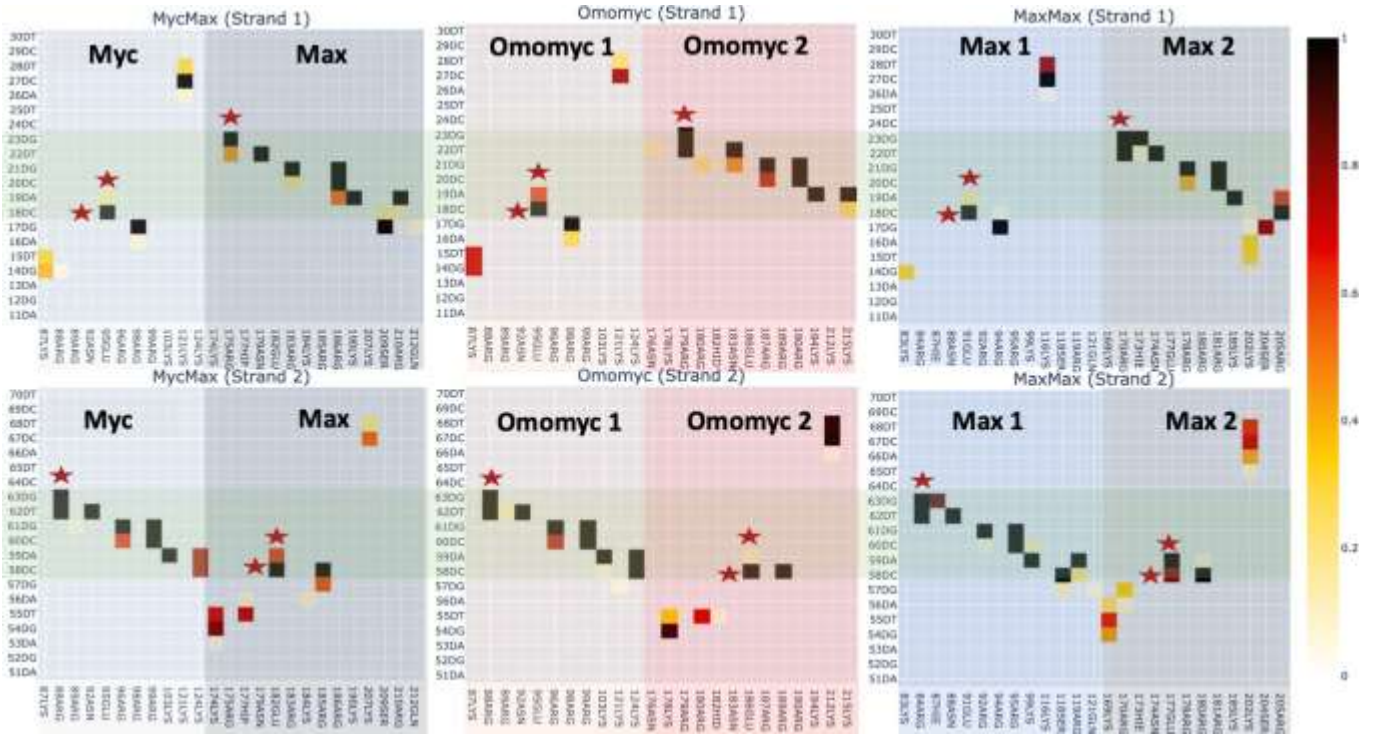
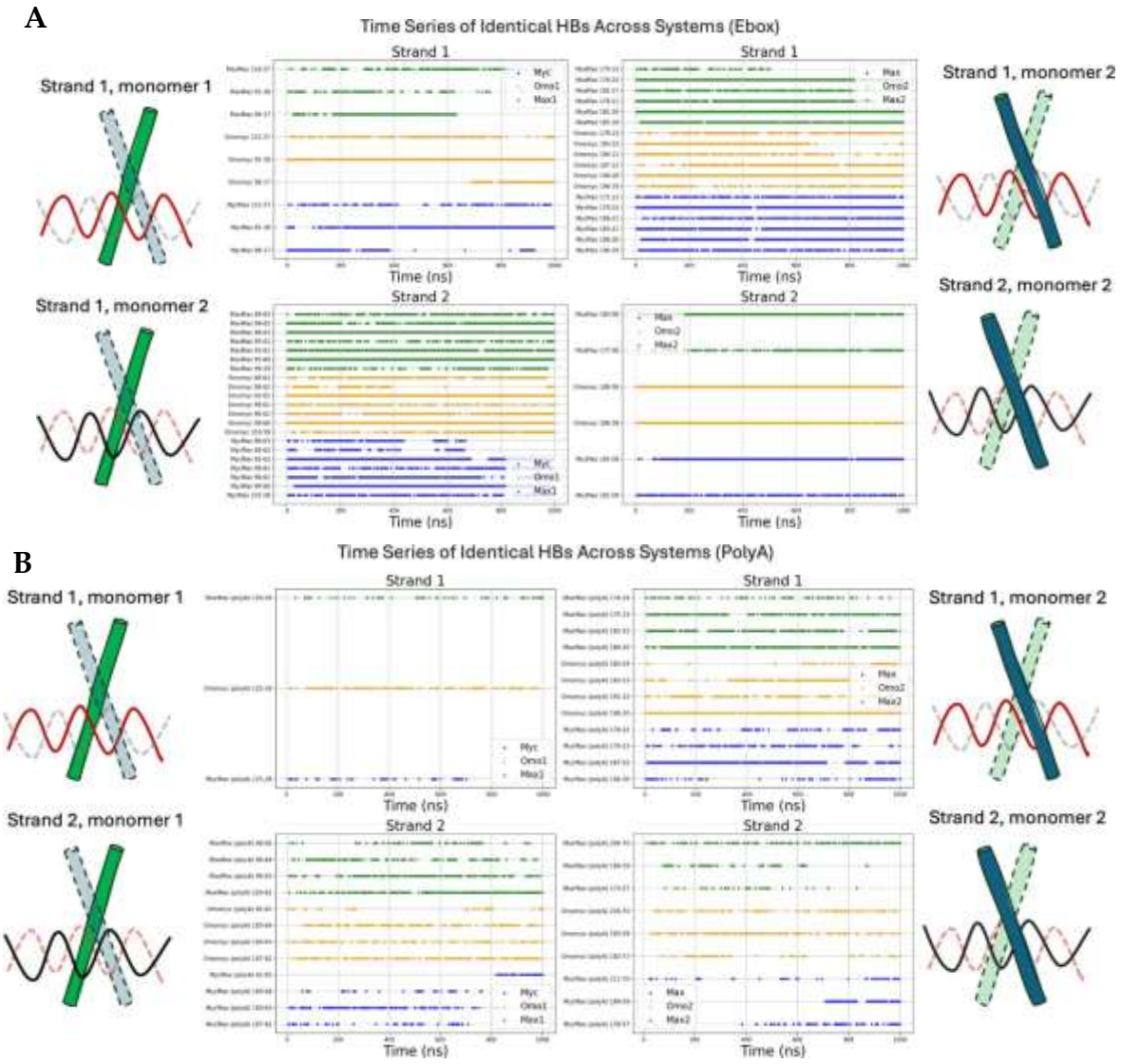


Figure S15: Hydrogen bonding or HB patterns from t=0-10 ns (top) and t=0-300 ns (bottom) for MycMax, Omomyc dimer and MaxMax complexes on E-box DNA. The heatmaps show unique protein-DNA residue contact occupancies for MycMax (left), Omomyc (middle) and MaxMax (right). The top row corresponds to contacts with DNA residues from Strand 1, bottom row corresponds to DNA residues from strand 2. Each co ntact map has the E-box region highlighted in green shade. Contacts belonging to each monomer are shaded with a diZerent color (light for first monome r, dark for second monomer). Contacts with DNA bases are marked by a star.



C

Ebox

DNA Strand 1						
DNA	MycMax-Myc	Omomyc-Omo1	MaxMax-Max1	MycMax-Max	Omomyc-Omo2	MaxMax-Max2
G[17]	R98	R98	R94	-	-	-
C[18]	E95	E95	E91	-	-	-
A[19]	-	-	-	K190	K194	K185
C[20]	-	-	-	R186	R190	R181
G[21]	-	-	-	R183	R187	R178
G[22]	-	-	-	R186	R190	R181
T[23]	-	-	-	N179	N183	N174
G[24]	-	-	-	R175	R179	R170
C[25]	K121	K121	K116	-	-	-

DNA Strand 2						
DNA	MycMax-Myc	Omomyc-Omo1	MaxMax-Max1	MycMax-Max	Omomyc-Omo2	MaxMax-Max2
C[26]	-	-	-	E182	E186	E177
C[27]	-	-	-	R185	R189	R180
A[28]	K103	K103	K99	-	-	-
C[29]	R99	R99	R95	-	-	-
G[30]	R96	R96	R92	-	-	-
G[31]	R99	R99	R95	-	-	-
T[32]	N92	N92	N88	-	-	-
T[33]	R88	R88	R84	-	-	-
G[34]	R88	R88	R84	-	-	-

PolyA

DNA Strand 1						
DNA	MycMax-Myc	Omomyc-Omo1	MaxMax-Max1	MycMax-Max	Omomyc-Omo2	MaxMax-Max2
A[19]	-	-	-	-	-	-
A[20]	-	-	-	K190	K194	K185
A[21]	-	-	-	-	-	-
A[22]	-	-	-	R183	R187	R178
A[23]	-	-	-	R175	R179	R170
A[24]	-	-	-	R175	R179	R170
A[25]	-	-	-	-	-	-
A[26]	K121	K121	K116	-	-	-

DNA Strand 2						
DNA	MycMax-Myc	Omomyc-Omo1	MaxMax-Max1	MycMax-Max	Omomyc-Omo2	MaxMax-Max2
T[27]	-	-	-	K174	K178	K169
T[28]	-	-	-	R185	R189	R180
T[29]	-	-	-	-	-	-
T[30]	K103	K103	K99	-	-	-
T[31]	R96	R96	R92	-	-	-
T[32]	R96	R96	R92	-	-	-
T[33]	R88	R88	R84	-	-	-
T[34]	-	-	-	K207	K212	K202

Figure S16: Time series plots showing the persistence of conserved HBs between protein residues and DNA strands in MycMax, Omomyc, and MaxMax bound to Ebox (A) or PolyA (B) over the 1 μs simulation period. Interactions from Myc are colored in blue, Omomyc in orange, and MaxMax in green. The plots are divided into interactions involving Strand 1 (top) and Strand 2 (bottom) with Protein 1 (left) and Protein 2 (right). Schematic representations are shown of the protein-DNA interactions for each strand and protein combination. (C) Tables summarizing the conserved HBs between DNA nucleotides and conserved protein residues for each complex. The tables list the DNA position, the interacting protein residues, and the complexes in which these interactions are observed. The Ebox systems are shown on the left, and the polyA systems on the right.

Count of unique atom pairs making HB contacts:

Ebox

	Ebox	Flank	Total
MycMax	33	13	46
Omomyc	41	8	49
MaxMax	32	13	45

polyA

	Center	Flank	Total
MycMax	19	15	34
Omomyc	29	11	40
MaxMax	34	11	45

Figure S17: Count of unique protein-DNA atoms pairs making HB contacts in the Ebox system (left) and polyA system (right) acrossthe 1-microsecond trajectory. Ebox and Center are the 6-bp central binding sites in the Ebox and polyA systems respectively, and Flank are the flanking DNA sites.

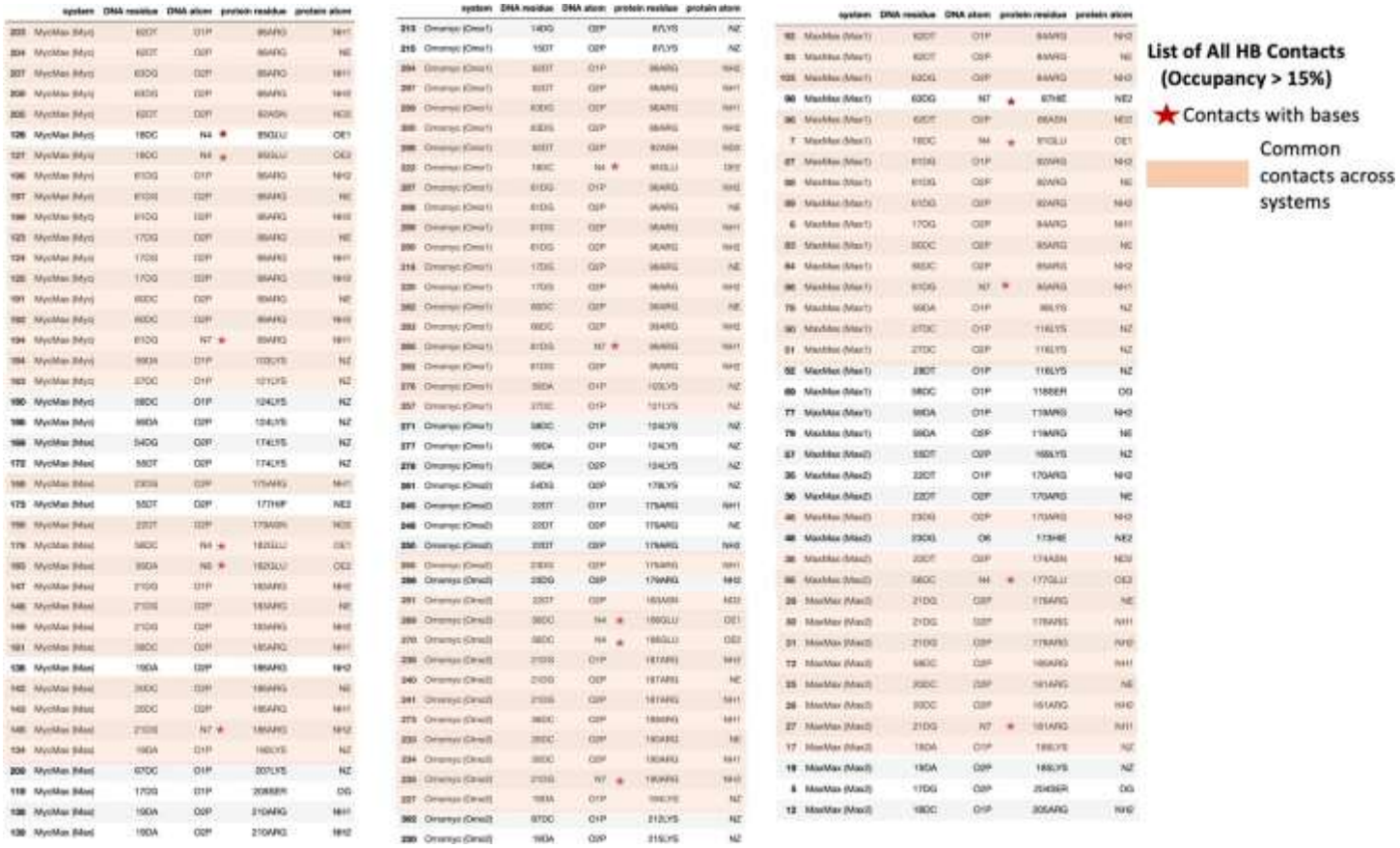


Figure S18: Unique HBs between protein and Ebox DNA atoms up until t=300ns. Contacts with bases are marked with a star, and the contacts that are common across all 3 systems at the atomic level are highlighted in pink.

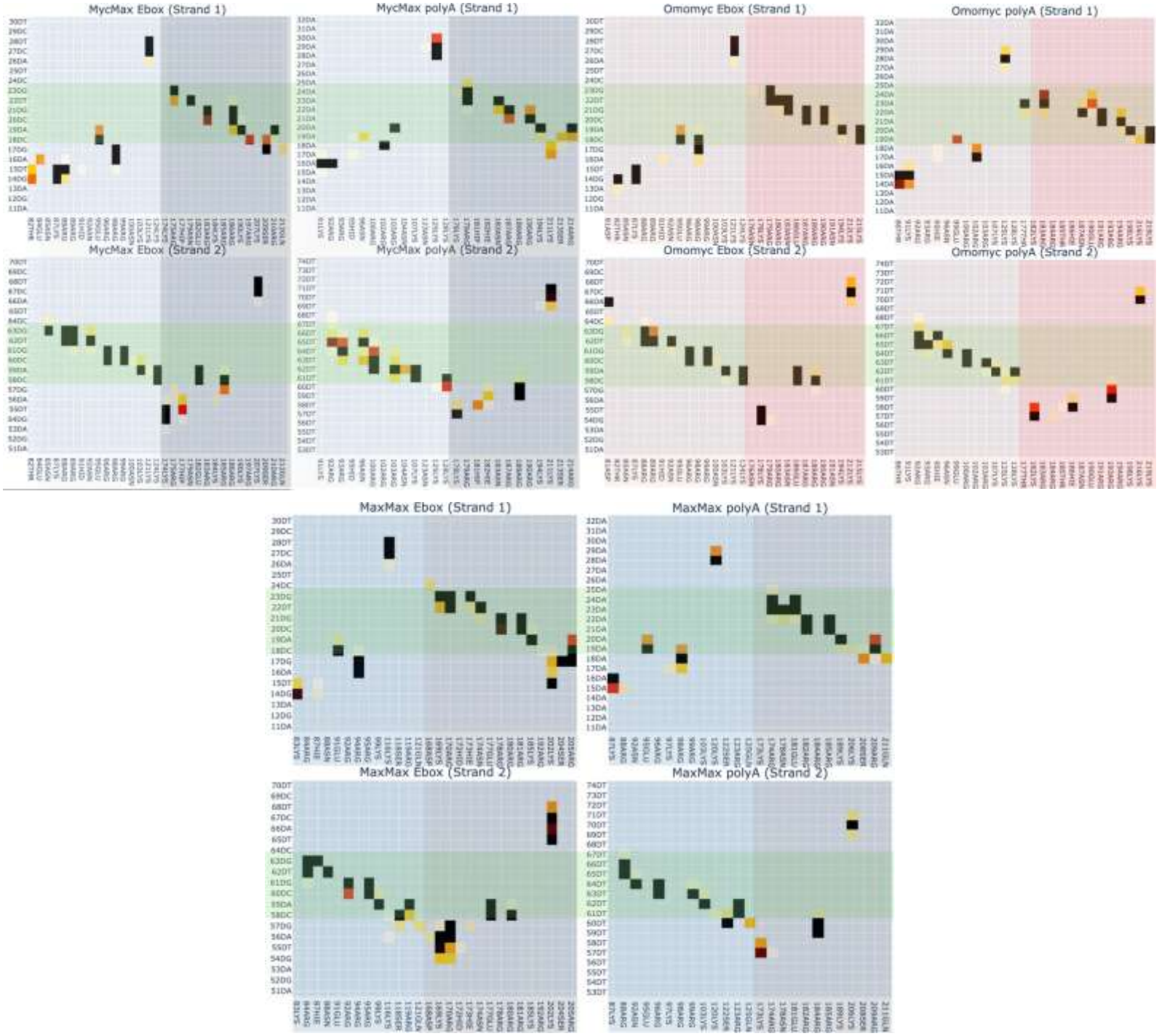


Figure S19: Comparing heatmaps of HB occupancy between Ebox and PolyA for MycMax (top left), Omomyc (top right), and MaxMax (bottom) from individual 1-us MD simulations. E-box region is highlighted in green, and each protein monomer is delimited by a rectangular colored box.

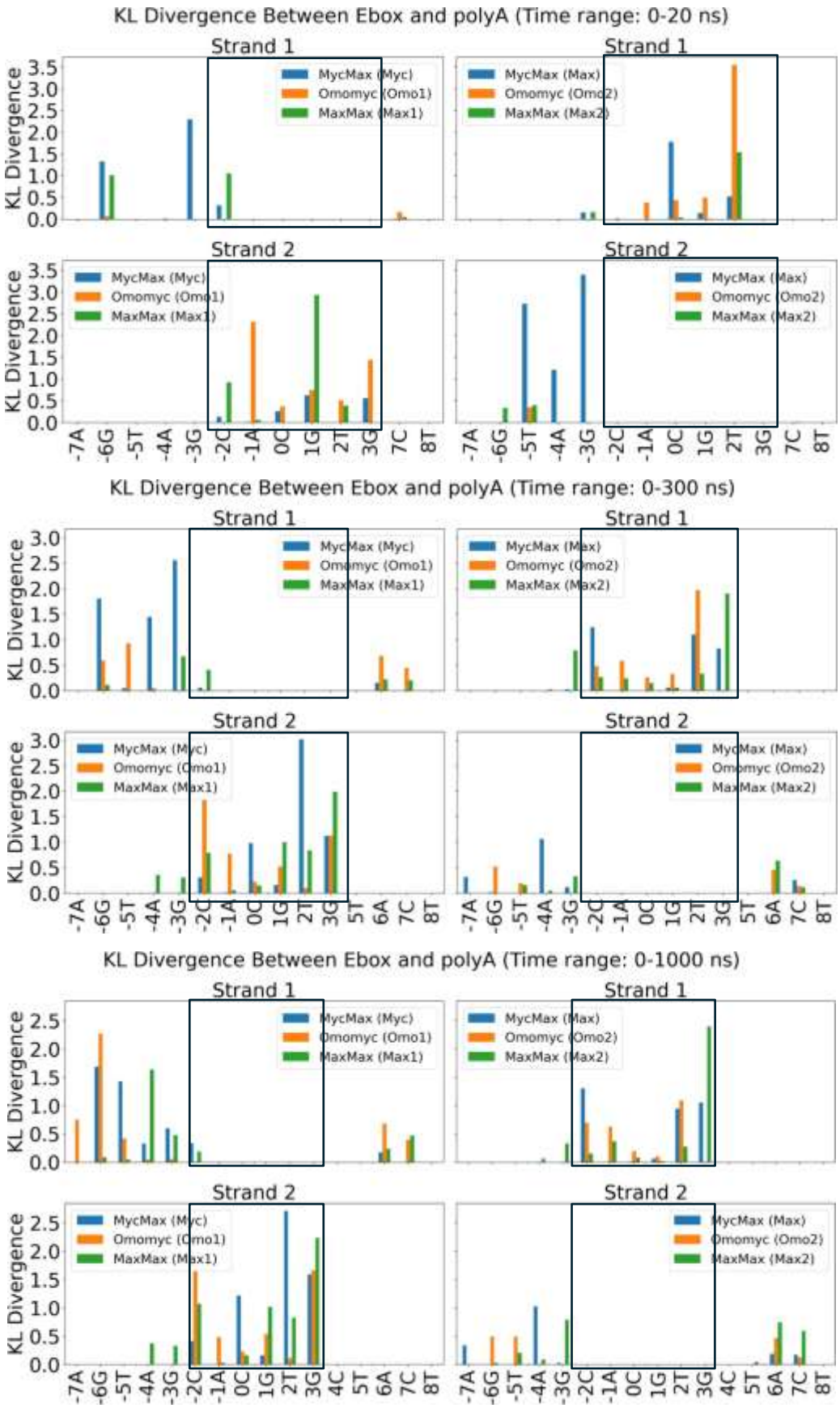


Figure S20: Comparison of MycMax, Omomyc dimer, and MaxMax interactions with E-box and PolyA. (A) KL divergence between E-box and polyA binding modes for MycMax (blue), Omomyc (orange), and MaxMax (green) complexes across both DNA strands over the 20 ns (top), 300 ns (middle), and 1μs trajectory (bottom). The E-box region is highlighted by the black box.