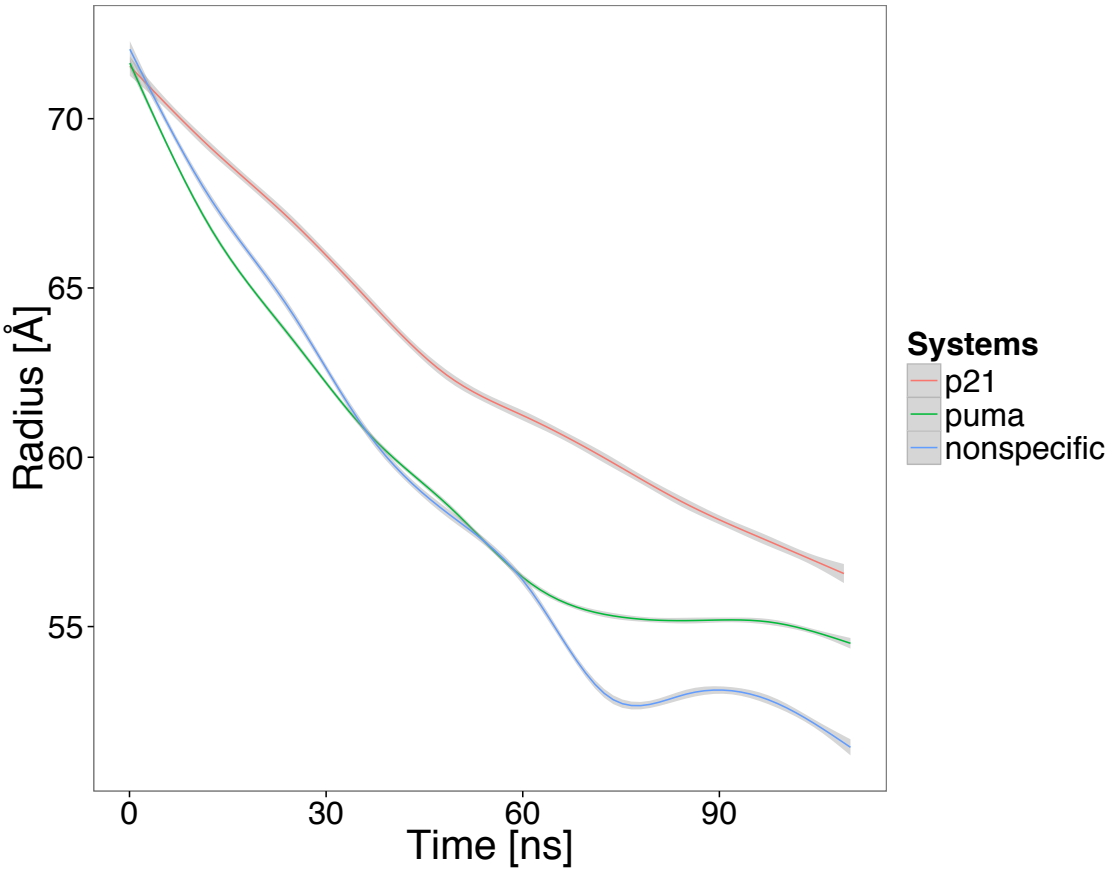
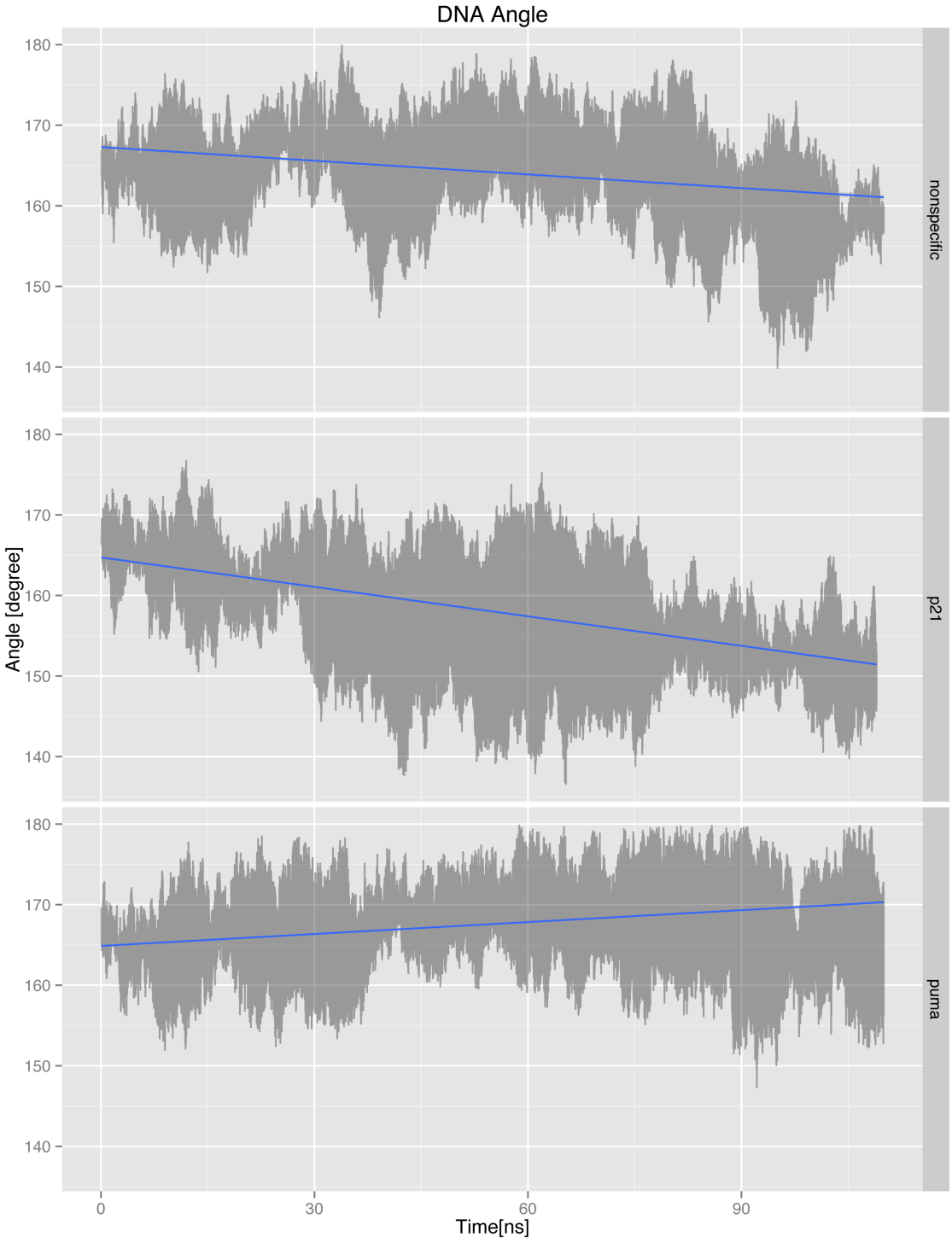
Supporting Information

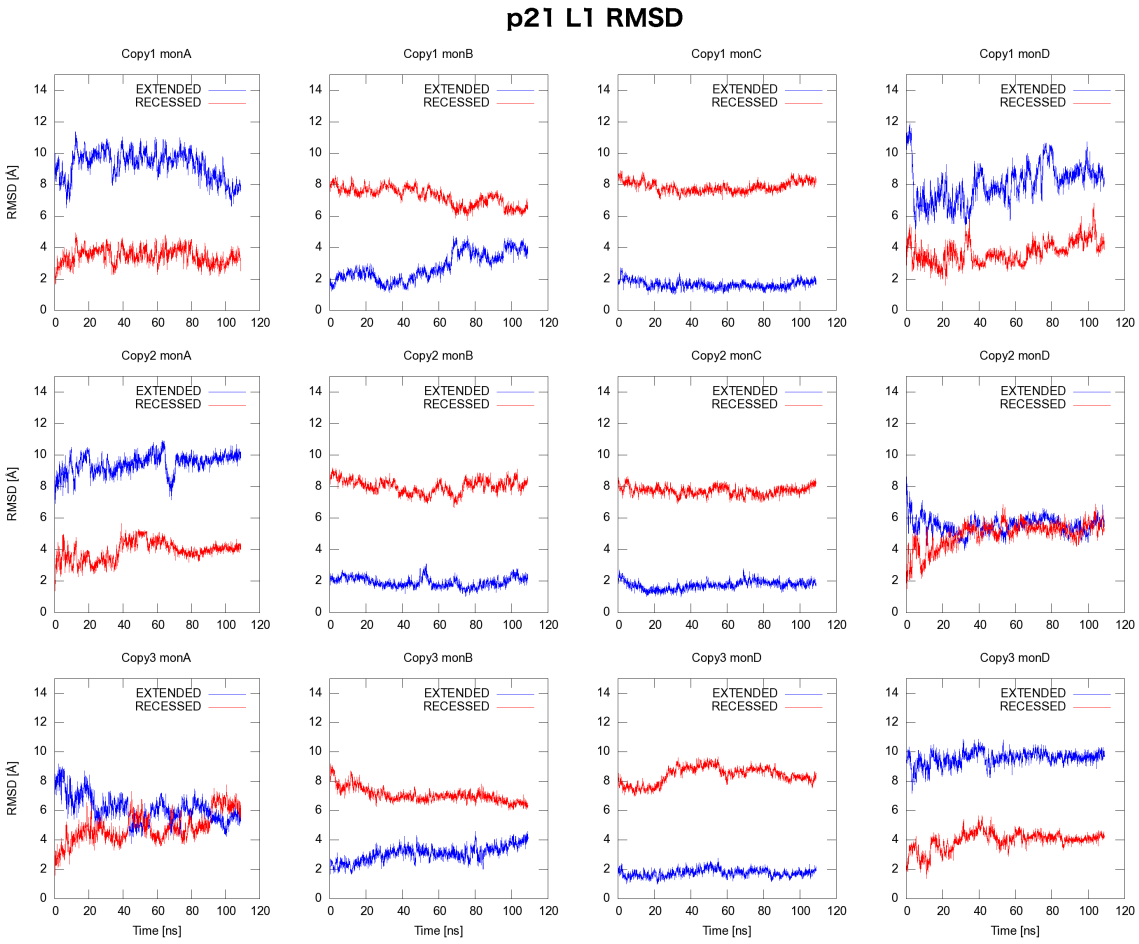
SI Materials and Methods



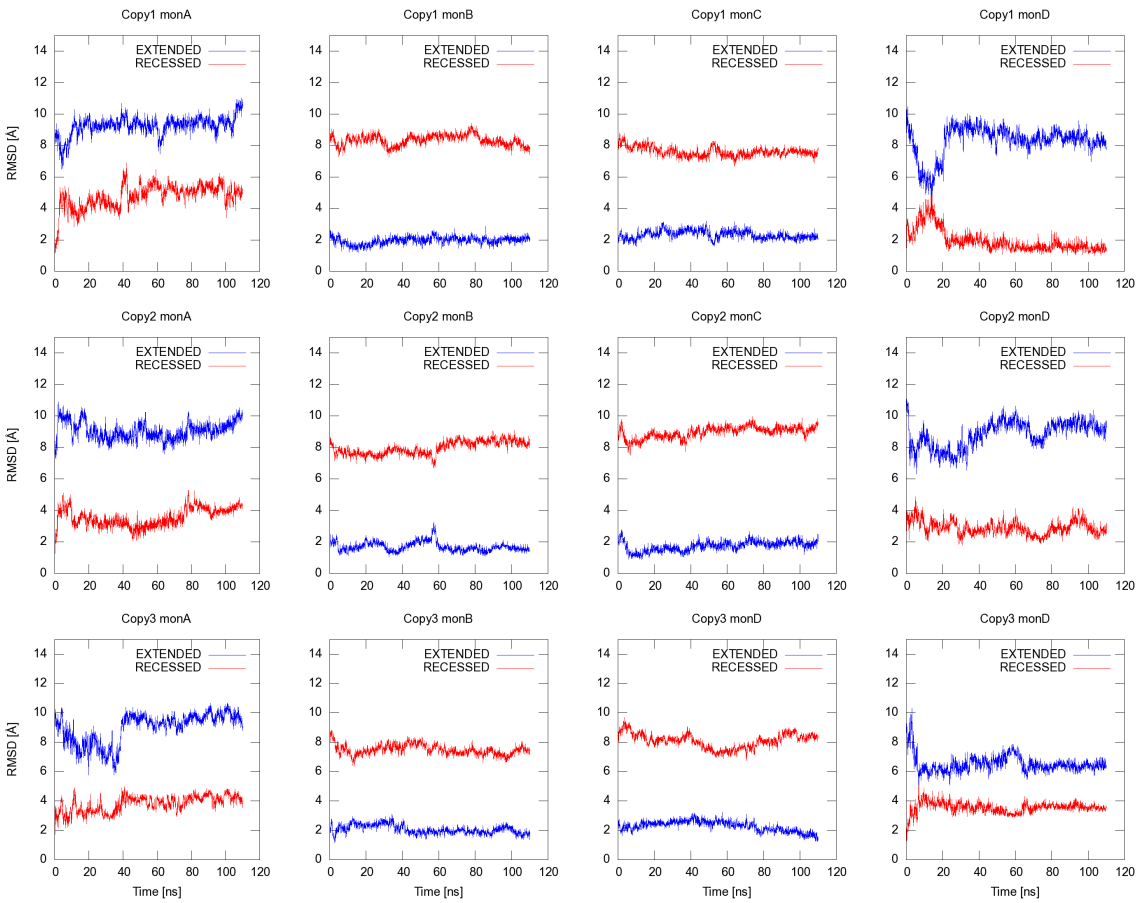
Supplementary Figure 1. Time evolution of the radius of gyration for the fl-p53.



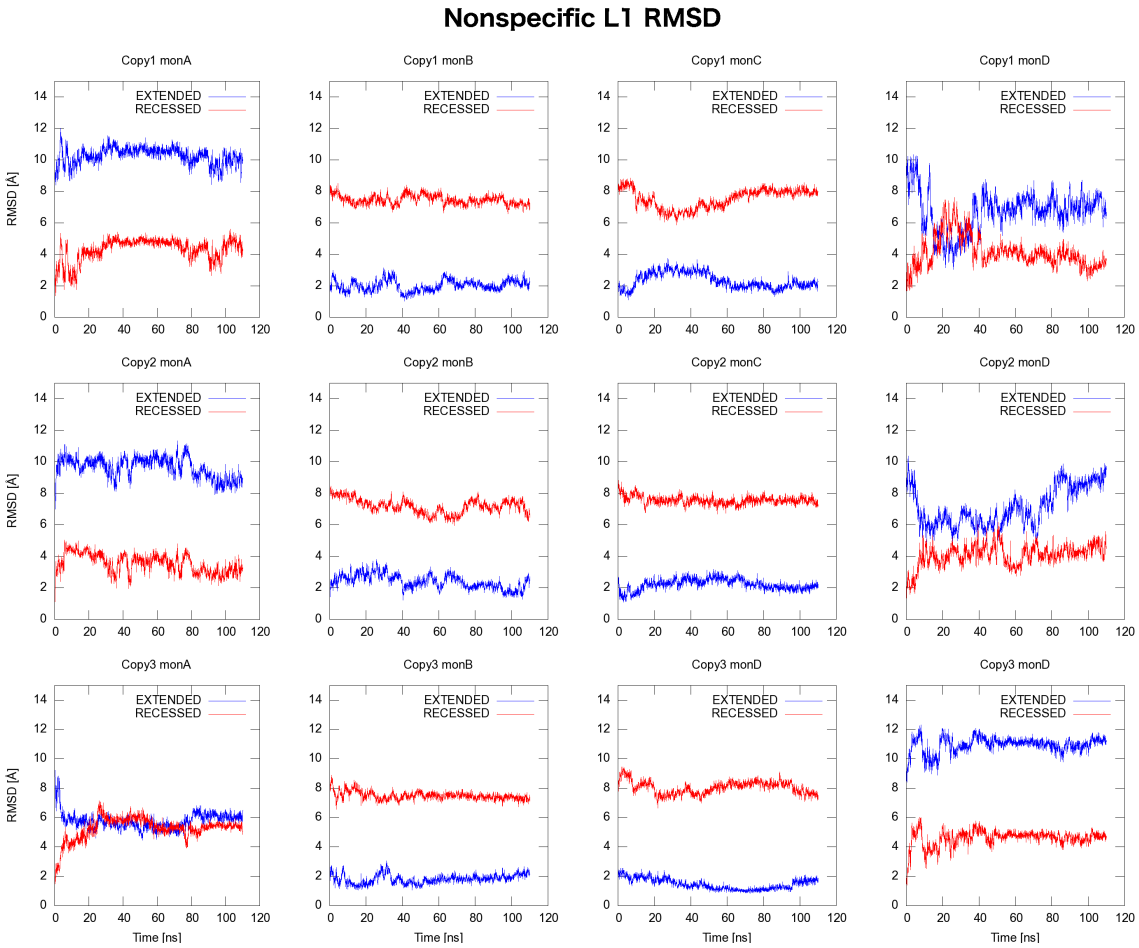
Supplementary Figure 2. Time evolution of the DNA bending angle in the three systems. The DNA bending angles of all three MD copies are combined and shown in dark gray. Blue Linear regression lines are drawn to show the bending trend for all copies of each system.



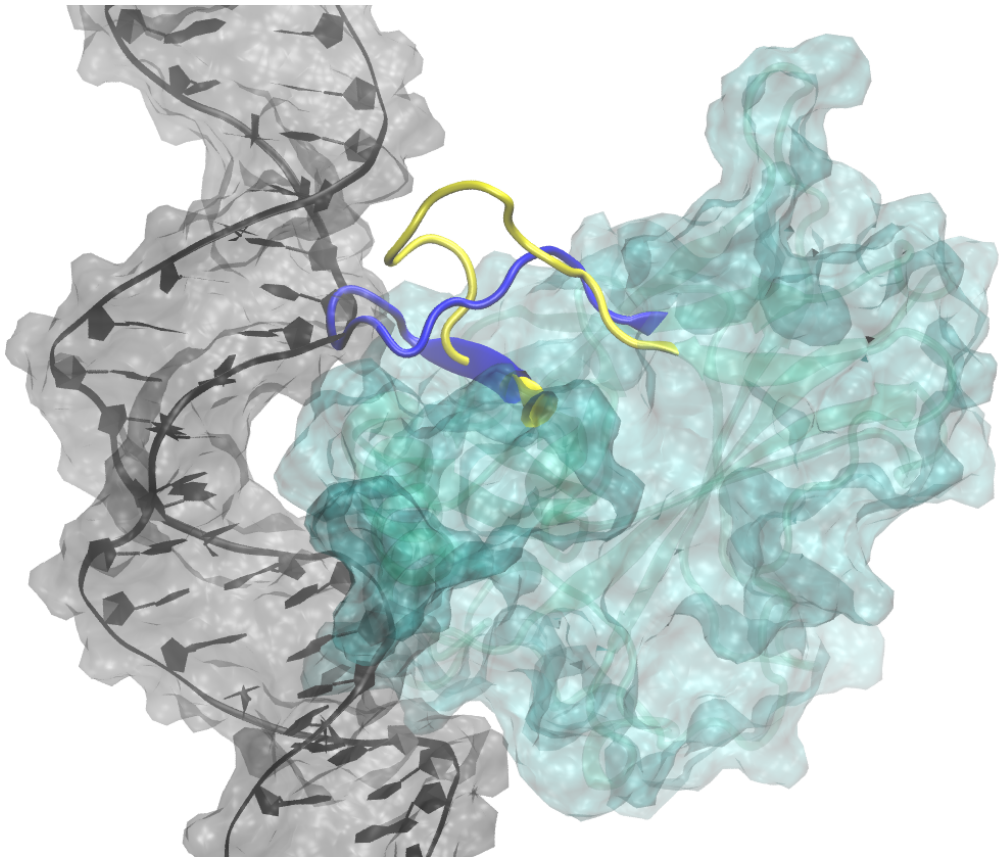
Supplementary Figure 3. L1 loop RMSD with respect to extended and recessed loop conformations in the p21 RE system. Time evolution of the rmsd of the L1 loop (of each p53 monomer in each MD copy) calculated with respect to both the extended and the recessed L1 loop conformations. The rmsd values calculated with respect to the extended and recessed L1 conformations are colored in blue and red, respectively.



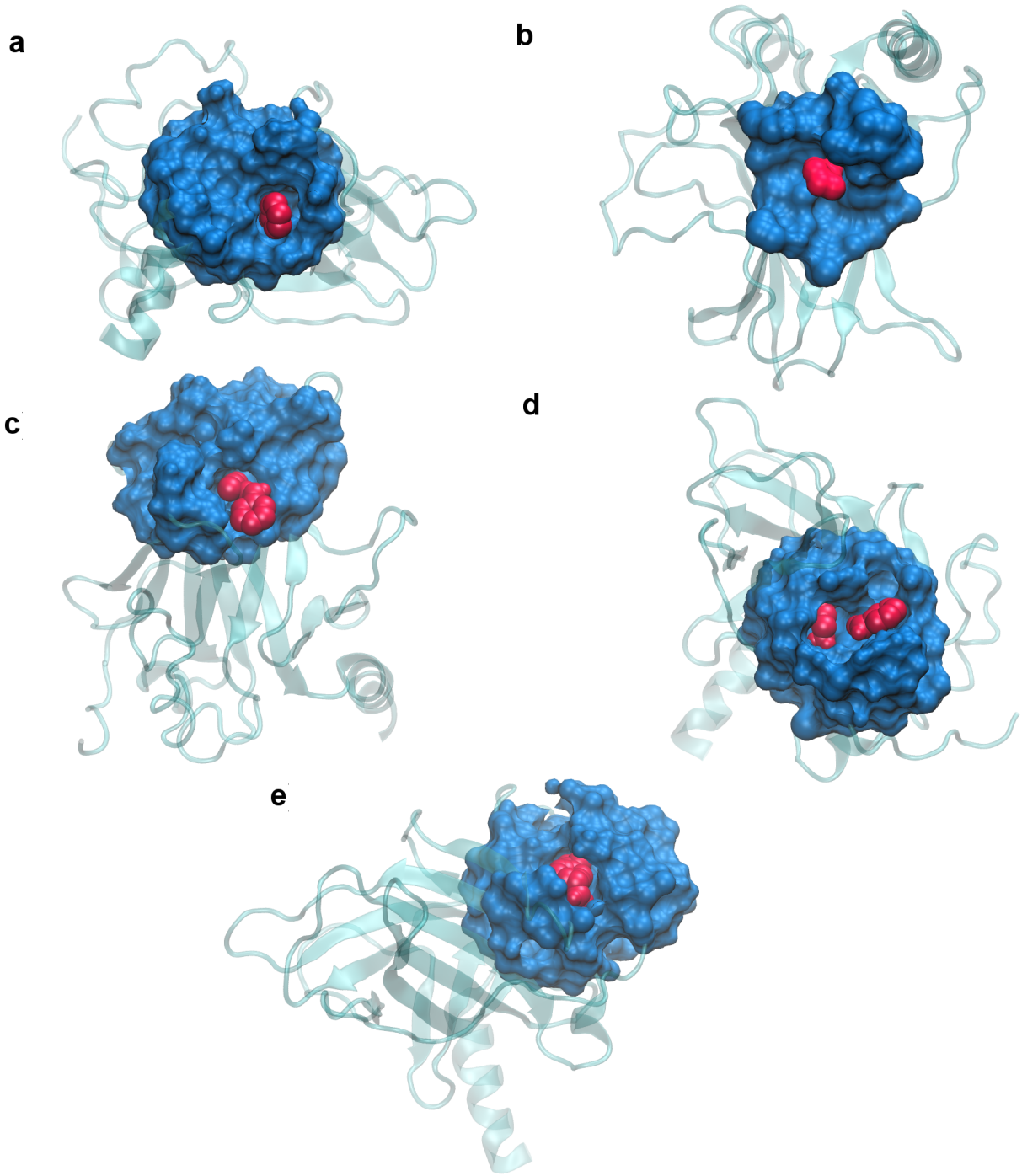
Supplementary Figure 4. L1 loop RMSD with respect to extended and recessed loop conformations in the puma RE system. Time evolution of the rmsd of the L1 loop (of each p53 monomer in each MD copy) calculated with respect to both the extended and the recessed L1 loop conformations. The rmsd values calculated with respect to the extended and recessed L1 conformations are colored in blue and red, respectively.



Supplementary Figure 5. L1 loop RMSD with respect to extended and recessed loop conformations in the nonspecific DNA system. Time evolution of the rmsd of the L1 loop (of each p53 monomer in each MD copy) calculated with respect to both the extended and the recessed L1 loop conformations. The rmsd values calculated with respect to the extended and recessed L1 conformations are colored in blue and red, respectively.



Supplementary Figure 6. Extended L1 Loop steric clash with the DNA in the outer monomer. The extended L1 loop conformation is superimposed onto an outer DBD monomer, which usually adopted a recessed L1 loop conformation. Only one monomer surface is shown in cyan. The native recessed L1 loop conformation is colored yellow while the superimposed extended L1 loop conformation is colored blue. The DNA is drawn in gray surface and the backbone is shown in ribbon representation. The blue extended L1 loop conformation overlaps with the DNA as shown in the above figure, indicating an unfavorable steric clash that will force the L1 loop to a recessed conformation.



Supplementary Figure 7. Computationally predicted druggable sites. a) the L1/S3 pocket, b) the L1 loop back pocket, c) the Tyr220 pocket, d) the Met160 pocket, and e) the Gln192 pocket are all drawn in blue surfaces. Small organic probe molecules are shown in each pocket to highlight the cavity.

copy1	% interaction	DNA counterpart	copy2	% interaction	DNA counterpart	copy3	% interaction	DNA counterpart
p21								
370	19.3%	DT1686, DT1687						
373	10.5%	DT1687, DT1686						
379	29.8%	DA1689						
381	25.0%	DA1689						
382	17.1%	DT1687						
puma								
370	7.1%	DA1591, DC1592	363	6.9%	DA1623	370	27.7%	DC1685, DT1686
372	21.5%	DT1686				373	10.5%	DC1685, DG1684
373	11.3%	DT1687				379	4.5%	DC1685
379	30.5%, 18.6%	DA1590, DC1589				381	19.2%	DC1685, DT1686
381	23.8%	DA1697						
382	21.8%	DA1591						
nonspecific								
			379	42.6%	DT1600	382	12.3%	DT1665
			381	50.8%	DT1600, DG1599	386	19.3%	DA1622, DT1666
			382	33.9%	DG1599	370	18.3%	DA1622, DA1621
			386	16.6%, 22.7%	DG1679, DG1678	372	6.1%	DT1666
						373	6.2%	DG1656
						363	8.4%	DA1630
						381	25.3%	DT1688
						382	44.2%	DT1600
						386	17.2%	DT1688, DG1598

Supplementary Table 1. Salt bridge footprint analysis. This table lists the percentage of salt bridge interactions between the C-terminal residues and the DNA in each MD copy for the three systems. The residues highlighted in blue, green and orange are from monomers A, B and C, respectively. The DNA nucleotides that each p53 residue interacted with are shown in the DNA counterpart column.

monomer	ResID	p21	puma	nonspecific
A	Ala276	43.0	18.7	0.0
B	Ala276	47.8	0.0	7.4
C	Ala276	60.1	49.1	22.0
D	Ala276	28.7	35.4	8.4
A	Arg280	44.3	37.1	9.1
B	Arg280	56.7	40.1	0.0
C	Arg280	69.9	44.9	16.9
D	Arg280	35.0	48.0	11.5
A	Ser241	61.3	67.9	60.9
B	Ser241	37.4	55.5	33.9
C	Ser241	62.7	69.8	40.8
D	Ser241	49.9	51.5	39.7
A	Arg273	43.8	60.1	26.5
B	Arg273	43.5	32.2	36.0
C	Arg273	52.9	47.5	36.5
D	Arg273	53.1	41.1	21.6
A	Asn239	39.2	23.6	4.7
B	Asn239	42.0	19.2	15.0
C	Asn239	46.6	36.5	25.8
D	Asn239	29.7	15.8	6.4
A	Ser121	26.6	32.4	17.4
B	Ser121	60.1	90.5	29.0
C	Ser121	42.9	28.3	91.7
D	Ser121	19.3	16.2	15.5
A	Lys120	19.3	9.7	0.0
B	Lys120	62.6	5.5	21.1
C	Lys120	61.9	48.1	5.1
D	Lys120	0.0	16.0	0.0
A	Arg248	23.8	28.9	9.7
B	Arg248	13.5	7.2	9.8
C	Arg248	17.6	40.9	4.8
D	Arg248	16.0	14.5	38.3
A	Thr123	8.0	35.8	0.0
B	Thr123	0.0	0.0	0.0
C	Thr123	0.0	0.0	0.0
D	Thr123	0.0	22.1	29.2
A	Asn288	13.8	20.4	10.8
B	Asn288	3.5	22.7	15.9
C	Asn288	5.3	12.1	3.4
D	Asn288	0.0	22.6	7.8

Supplementary Table 2. Hydrogen bond footprint analysis between the DNA and the fl-p53 tetramer. The average scores of the key protein residues in the four p53 monomers in each system are shown.

p21

	monA	monB	monC	monD
Copy1	94.77	7.35	10.06	94.67
Copy2	94.97	23.14	9.05	95.61
Copy3	33.87	6.68	6.04	98.63

puma

	monA	monB	monC	monD
Copy1	81.66	10.08	4.77	99.64
Copy2	96.78	8.08	73.45	96.6
Copy3	99.64	16.07	11.03	97.19

nonspecific DNA

	monA	monB	monC	monD
Copy1	95.9	6.33	11.65	18.62
Copy2	93.19	21.83	7.08	6.35
Copy3	5.54	13.94	24.57	91.78

Supplementary Table 3. Percentage of L1/S3 pocket open conformations for each monomer during MD simulations of the three systems.

Supplementary Movie 1. PC1 motion from the protein alpha carbons illustrating the C-terminal motion going from an extended to a compact conformation.

Supplementary Movie 2. PC1 motion of the DBD tetramer going from minimum to maximum PC1 values. Only p53 DBDs and DNA are depicted.

Supplementary Movie 3. PC2 motion of the DBD tetramer going from minimum to maximum PC2 values. Only p53 DBDs and DNA are depicted.