

Supplementary Material

This file contains supplementary tables and figures associated to the paper *On the variation of structural divergence among residues in enzyme evolution*, by J. Echave and M. Carpentier.

Dataset

Table S1: Dataset entries and reference protein

M-CSA	PDB	Name	Source	Family
2	1btl_A	Beta-lactamase TEM	Escherichia coli	Class-A beta-lactamase family
15	1znb_A	Metallo-beta-lactamase type 2	Bacteroides fragilis	Metallo-beta-lactamase superfamily
71	1eug_A	Uracil-DNA glycosylase	Escherichia coli B	Uracil-DNA glycosylase (UDG) superfamily
98	1bsz_C	Peptide deformylase	Escherichia coli K-12	Polypeptide deformylase family
109	1d3g_A	Dihydroorotate dehydrogenase (quinone), mitochondrial	Homo sapiens	Dihydroorotate dehydrogenase family
148	1onr_A	Name not found	Escherichia coli	Transaldolase family
151	1q0n_A	2-amino-4-hydroxy-6-hydroxymethyldihydropteridine pyrophosphokinase	Escherichia coli	HPPK family
160	1ako_A	Exodeoxyribonuclease III	Escherichia coli K-12	DNA repair enzymes AP/ExoA family
164	1ruv_A	Ribonuclease pancreatic	Bos taurus	Pancreatic ribonuclease family
174	9pap_A	Papain	Carica papaya	Peptidase C1 family
216	1ca2_A	Carbonic anhydrase 2	Homo sapiens	Alpha-carbonic anhydrase family
252	1igs_A	Indole-3-glycerol phosphate synthase	Saccharolobus solfataricus	TrpC family
257	1xx2_A	Beta-lactamase	Enterobacter cloacae	Class-C beta-lactamase family
258	1sml_A	Metallo-beta-lactamase L1 type 3	Stenotrophomonas maltophilia	Metallo-beta-lactamase superfamily
290	1zio_A	Adenylate kinase	Geobacillus stearothermophilus	Adenylate kinase family
328	1lbn_A	N-(5'-phosphoribosyl)-L-tryptophan synthase	Thermotoga maritima	TrpF family
351	1snz_A	Galactose mutarotase	Homo sapiens	Aldose epimerase family
362	1d6o_A	Peptidyl-prolyl cis-trans isomerase FKBP1A	Homo sapiens	FKBP-type PPIase family
376	1a4l_A	Adenosine deaminase	Mus musculus	Metallo-dependent hydrolases superfamily
394	1aj0_A	Dihydropteroate synthase	Escherichia coli	DHPS family
444	1cel_A	Exoglucanase 1	Trichoderma reesei	Glycosyl hydrolase 7 (cellulase C) family
462	1pnt_A	Low molecular weight phosphotyrosine protein phosphatase	Bos taurus	Low molecular weight phosphotyrosine protein phosphatase family
467	1cv2_A	Haloalkane dehalogenase	Sphingomonas paucimobilis	Haloalkane dehalogenase family
480	1czf_A	Endopolygalacturonase II	Aspergillus niger	Glycosyl hydrolase 28 family
597	1uch_A	Ubiquitin carboxyl-terminal hydrolase isozyme L3	Homo sapiens	Peptidase C12 family
681	1gq8_A	Pectinesterase	Daucus carota	Pectinesterase family
693	2rnf_A	Ribonuclease 4	Homo sapiens	Pancreatic ribonuclease family
749	1nml_A	No information found	Marinobacter nauticus	No information found
814	1glo_A	Cathepsin S	Homo sapiens	Peptidase C1 family
858	1mrq_A	Aldo-keto reductase family 1 member C1	Homo sapiens	Aldo/keto reductase family
877	1pbg_A	6-phospho-beta-galactosidase	Lactococcus lactis	Glycosyl hydrolase 1 family
908	1rtu_A	Ribonuclease U2	Ustilago sphaerogena	Ribonuclease U2 family
923	2acy_A	Acylphosphatase-1	Bos taurus	Acylphosphatase family
931	2pth_A	Peptidyl-tRNA hydrolase	Escherichia coli K-12	PTH family

Table S2: Dataset properties

M-CSA	N	<Id%>	<RMSD>	Length	AS size	AS RMSD	CATH	EC
2	6	43	1.04	263	6	1.78	alpha/beta	Hydrolases
15	6	35	1.16	225	8	1.84	alpha/beta	Hydrolases
71	8	43	1.08	223	4	1.49	alpha/beta	Hydrolases
98	10	37	2.15	168	7	1.44	alpha/beta	Hydrolases
109	4	44	1.31	359	7	2.65	alpha/beta	Oxidoreductases
148	5	53	1.06	316	5	2.09	alpha/beta	Transferases
151	4	47	1.14	158	4	2.07	alpha/beta	Transferases
160	10	34	1.49	256	7	2.63	alpha/beta	Hydrolases
164	5	48	1.09	123	5	1.92	alpha/beta	Lyases
174	12	43	1.01	212	4	1.57	alpha/beta	Hydrolases
216	5	39	1.09	256	6	2.27	alpha/beta	Lyases
252	6	35	1.75	245	7	2.93	alpha/beta	Lyases
257	10	45	0.94	359	6	1.48	alpha/beta	Hydrolases
258	4	38	1.97	263	7	1.80	alpha/beta	Hydrolases
290	7	47	1.10	217	5	1.82	alpha/beta	Transferases
328	4	33	1.47	193	2	2.55	alpha/beta	Isomerases
351	4	33	1.36	341	3	2.65	all-beta	Isomerases
362	7	46	0.92	107	6	2.30	alpha/beta	Isomerases
376	4	44	1.30	349	6	2.42	alpha/beta	Hydrolases
394	10	40	2.02	280	2	2.35	alpha/beta	Transferases
444	6	46	1.19	431	4	2.12	all-beta	Hydrolases
462	6	37	1.15	155	6	1.81	alpha/beta	Hydrolases
467	5	45	1.03	293	5	1.90	alpha/beta	Hydrolases
480	4	44	1.05	335	6	1.86	all-beta	Hydrolases
597	4	38	1.76	204	4	3.15	alpha/beta	Hydrolases
681	4	31	2.88	300	5	6.68	all-beta	Hydrolases
693	7	38	1.62	120	3	2.20	alpha/beta	Hydrolases
749	6	56	1.96	316	1	3.89	all-alpha	NA
814	4	46	0.72	215	4	1.22	alpha/beta	Hydrolases
858	16	38	1.88	322	4	1.70	alpha/beta	Oxidoreductases
877	23	37	1.52	447	2	2.42	alpha/beta	Hydrolases
908	5	45	1.45	107	4	2.55	alpha/beta	Lyases
923	4	34	0.99	98	2	1.29	alpha/beta	Hydrolases
931	7	39	1.40	193	4	1.85	alpha/beta	Hydrolases

N: number of family members; <Id%>: average family seq. identity; <RMSD>: average family RMSD; Length: number of residues of reference protein; AS size: number of residues of active site; CATH: CATH class; EC: EC class

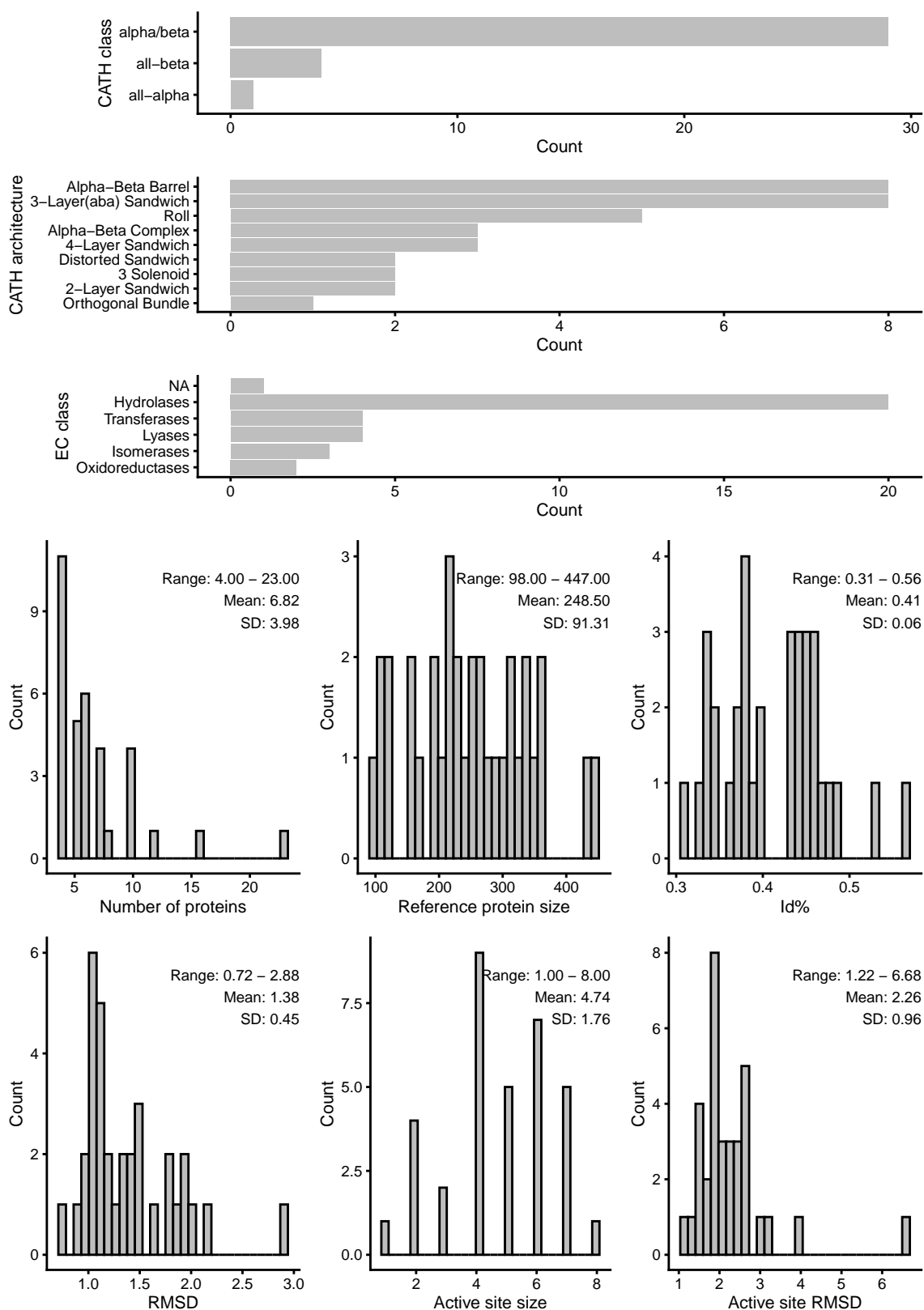


Figure S1: Distribution of properties of dataset families.

Correlation between flexibility and distance

The following figure shows the distribution of spearman correlations between flexibility (IRMSF) and distance to the active site (d) (panel a). The correlation between these variables depends on the location of the active site within the enzyme structure. In most cases active sites are located in relatively rigid regions. Therefore, as one moves away from the active site, not only distance increases but flexibility too, which originates the correlation (panel b).

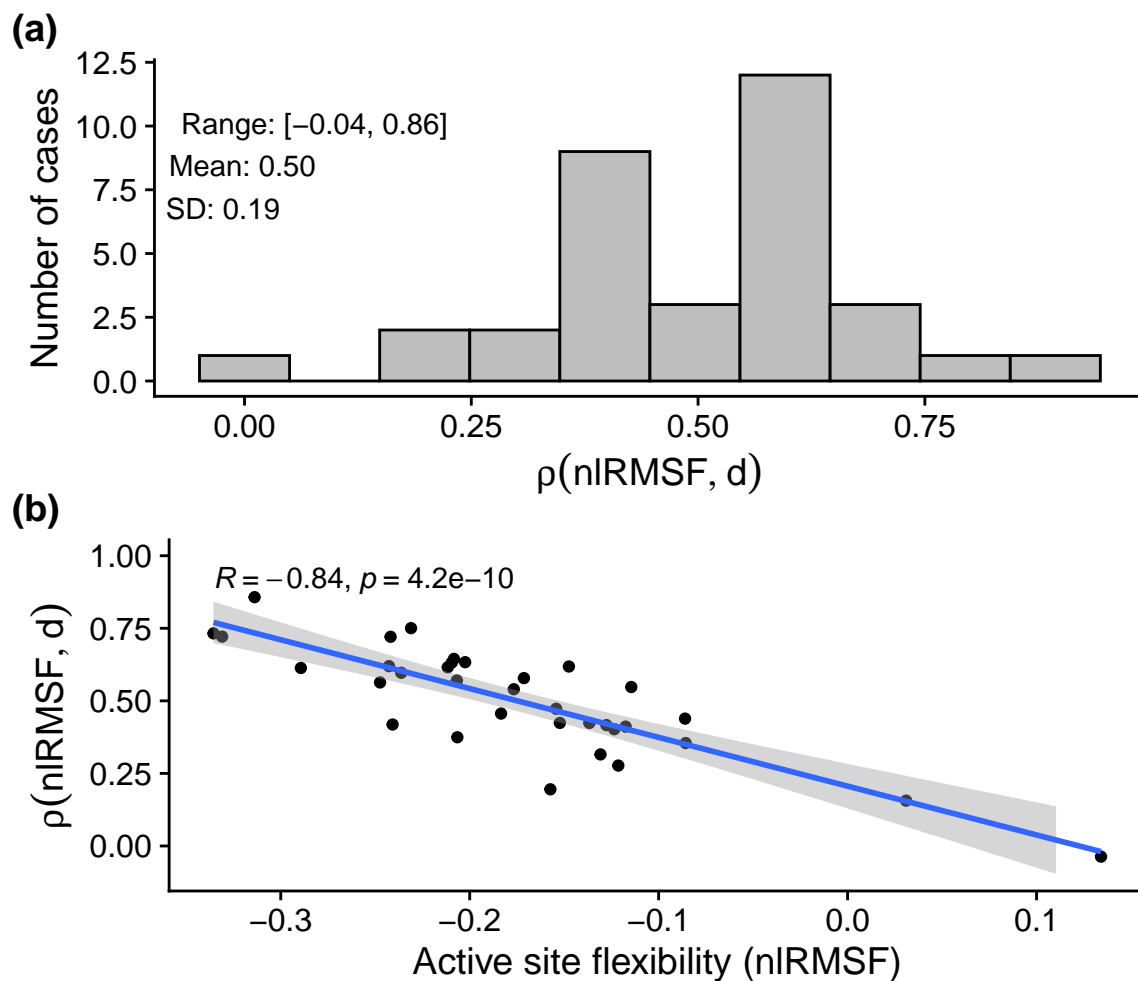


Figure S2: Correlation between flexibility and distance.

Family by family analysis

Figure Description

Each figure in this section represents a structural divergence analysis for a specific enzyme family, identified by its MCSA ID.

Each figure is organized as follows:

Observed patterns: (a) Residue-specific structural divergence profile, showing normalized log-RMSD (nlRMSD) across residues. (b) Relationship between structural divergence (nlRMSD) and residue flexibility (nlRMSF). (c) Relationship between structural divergence (nlRMSD) and distance from the active site (d).

Model predictions vs. observations: (d) Comparison of observed nlRMSD profile with predictions from models M1, M2, and M12. (e) Flexibility trends: observed data vs. model predictions for nlRMSD vs. nlRMSF. (f) Distance trends: observed data vs. model predictions for nlRMSD vs. d.

Decomposition into flexibility and distance contributions: (g) Profile of structural divergence decomposed into flexibility (s1) and distance (s2) components. (h) Flexibility (s1) component of structural divergence. (i) Distance (s2) component of structural divergence.

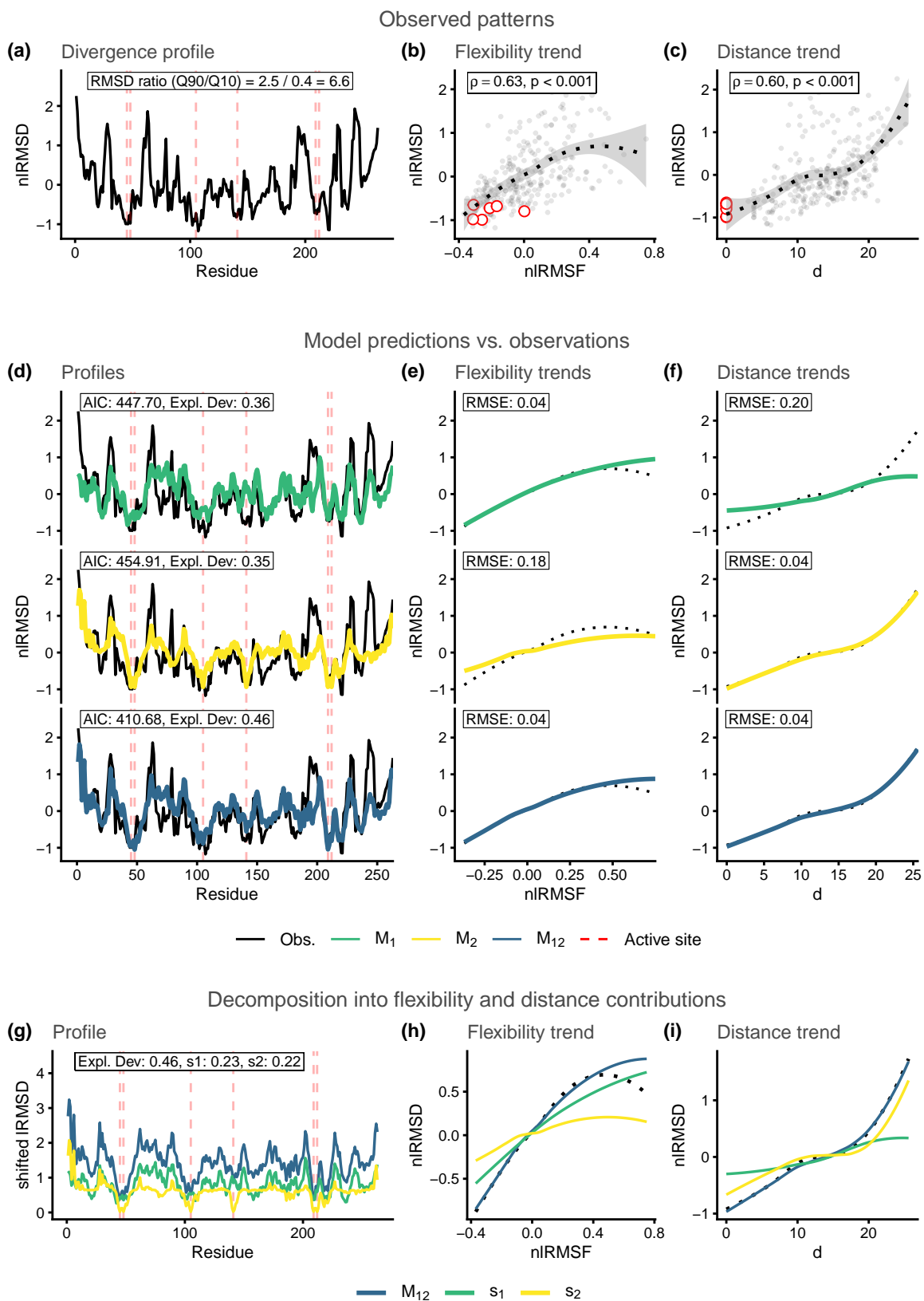


Figure S3: Structural divergence analysis for enzyme family MCSA ID: 2. Reference protein PDB ID: 1btl_A.

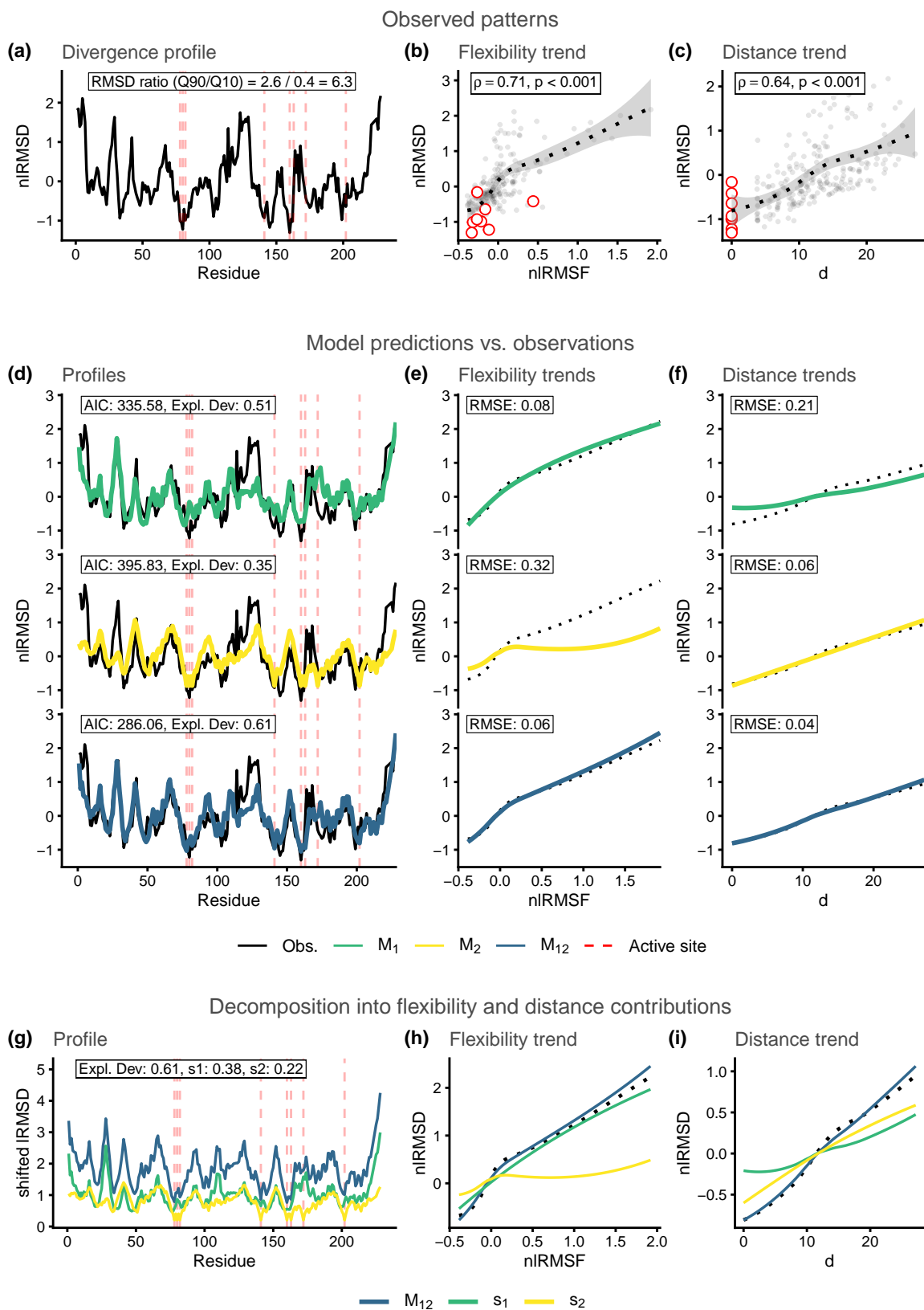


Figure S4: Structural divergence analysis for enzyme family MCSA ID: 15. Reference protein PDB ID: 1znb_A.

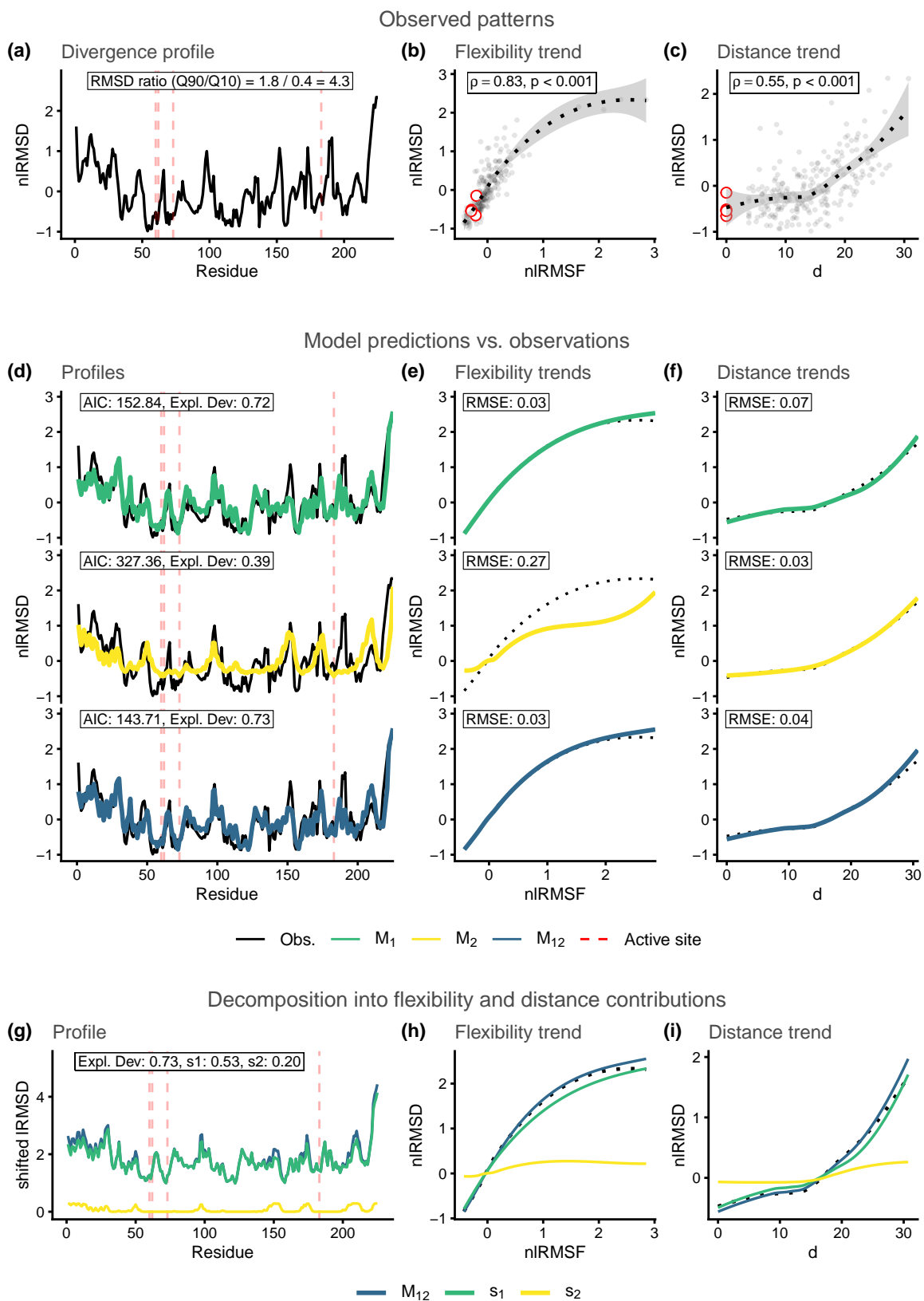


Figure S5: Structural divergence analysis for enzyme family MCSA ID: 71. Reference protein PDB ID: 1eug_A.

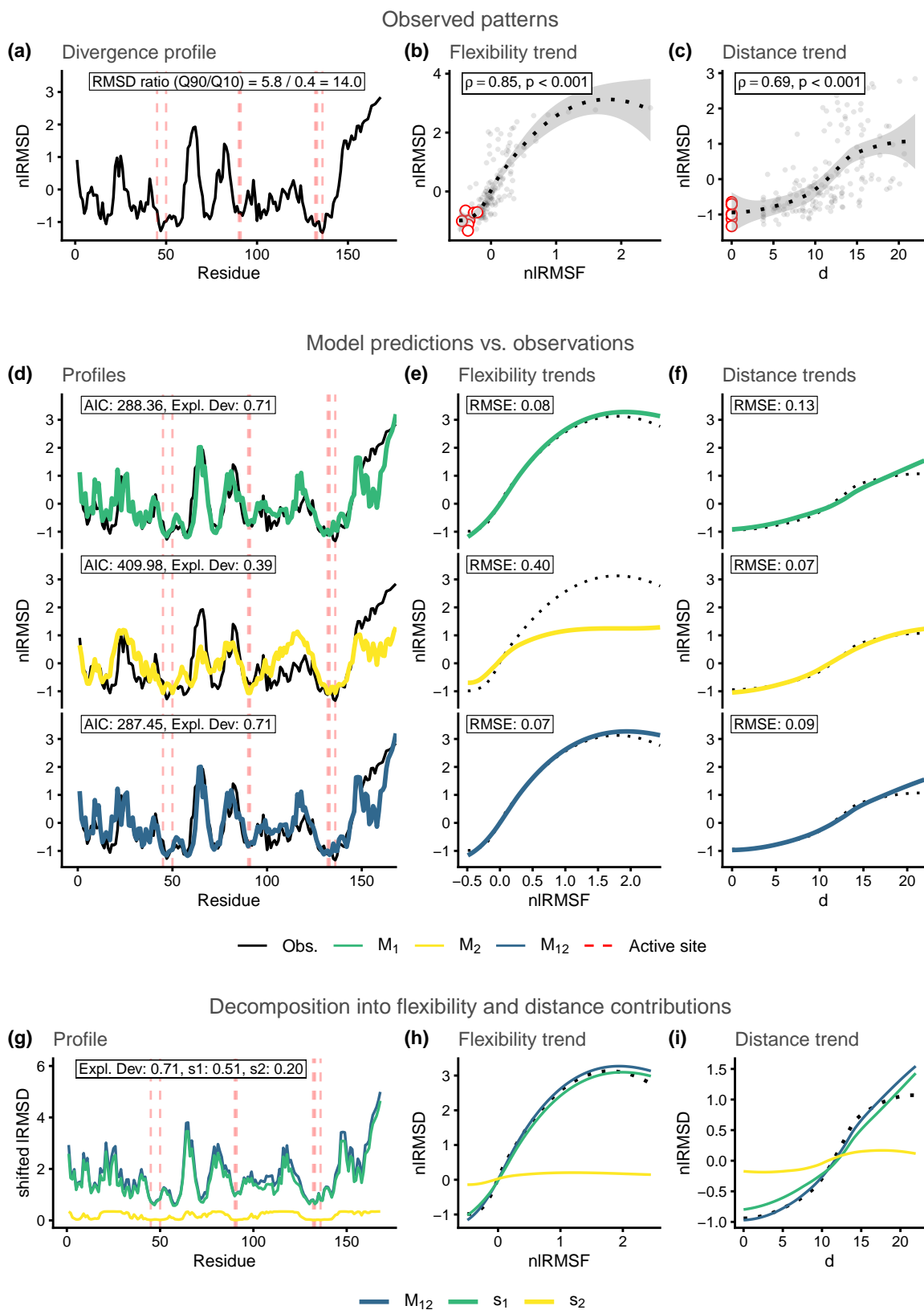


Figure S6: Structural divergence analysis for enzyme family MCSA ID: 98. Reference protein PDB ID: 1bsz_C.

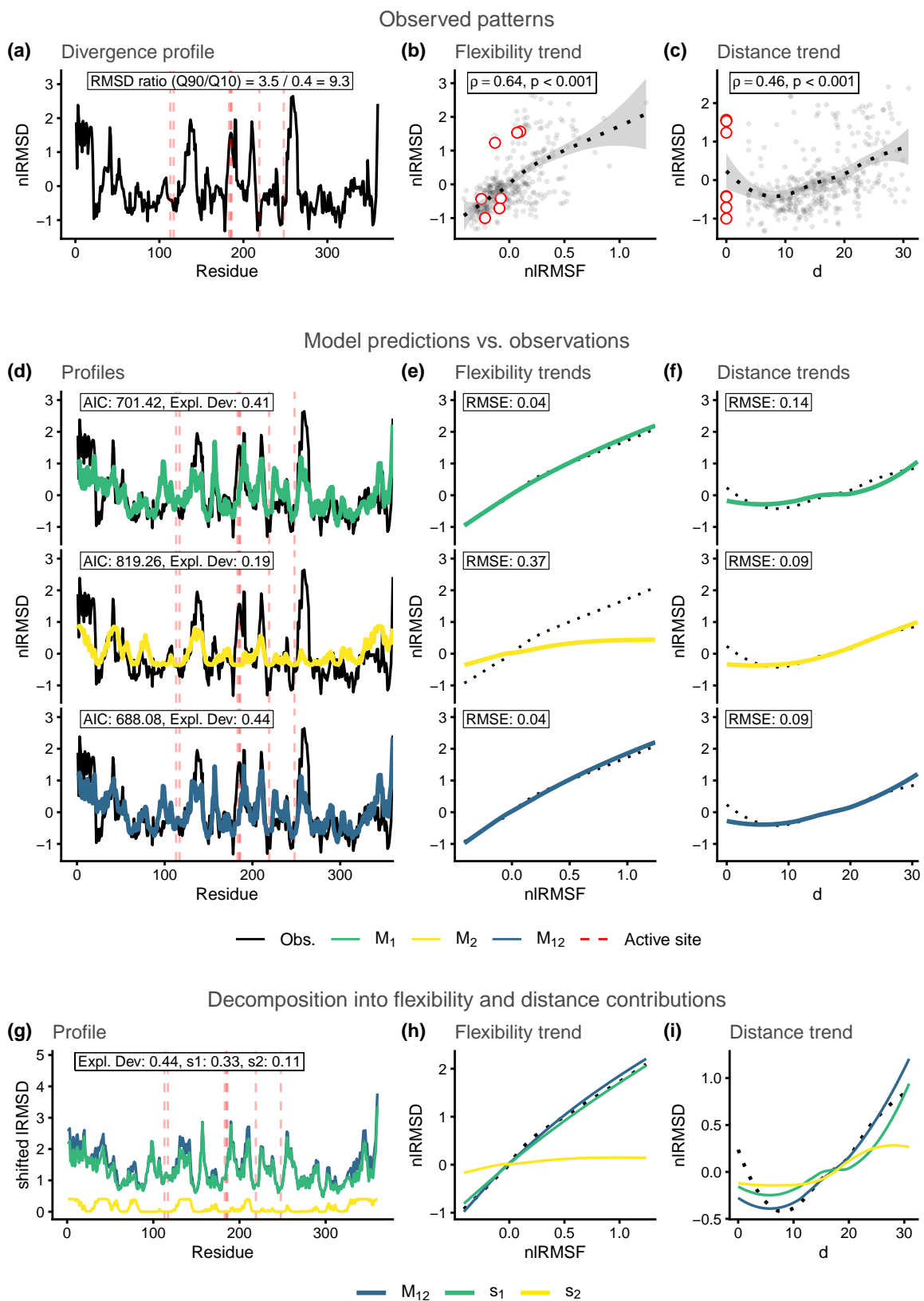


Figure S7: Structural divergence analysis for enzyme family MCSA ID: 109. Reference protein PDB ID: 1d3g_A.

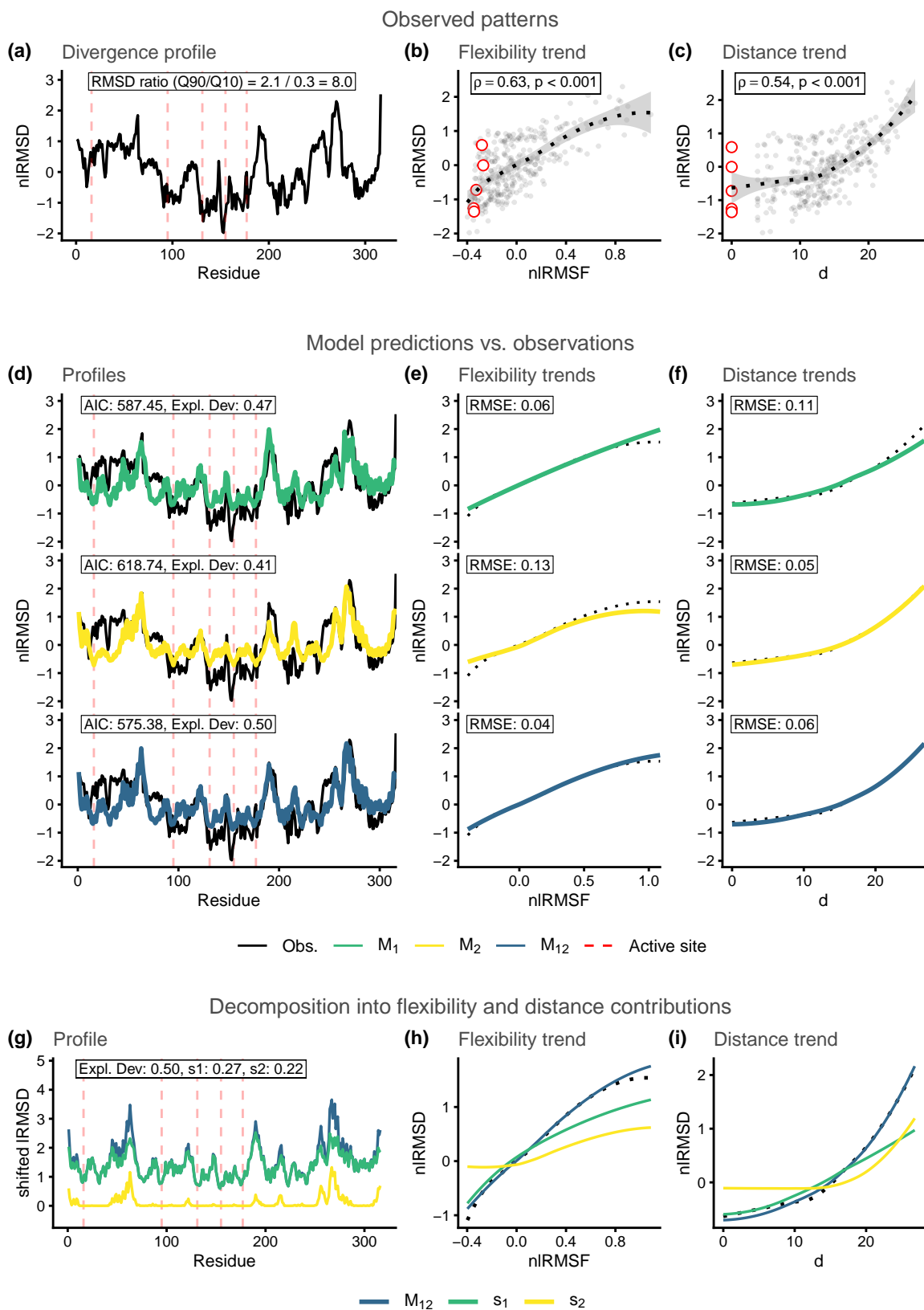


Figure S8: Structural divergence analysis for enzyme family MCSA ID: 148. Reference protein PDB ID: 1onr_A.

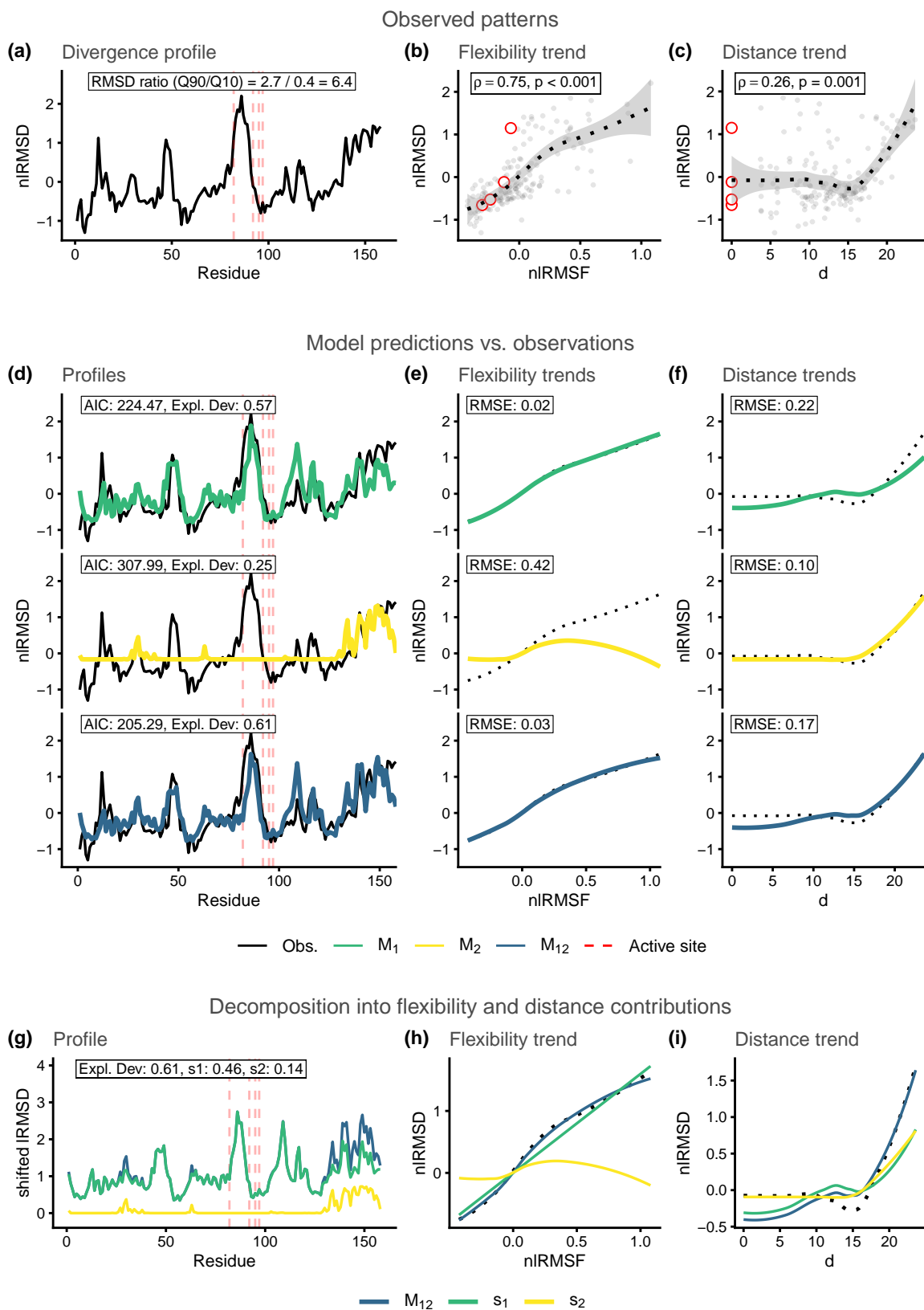


Figure S9: Structural divergence analysis for enzyme family MCSA ID: 151. Reference protein PDB ID: 1q0n_A.

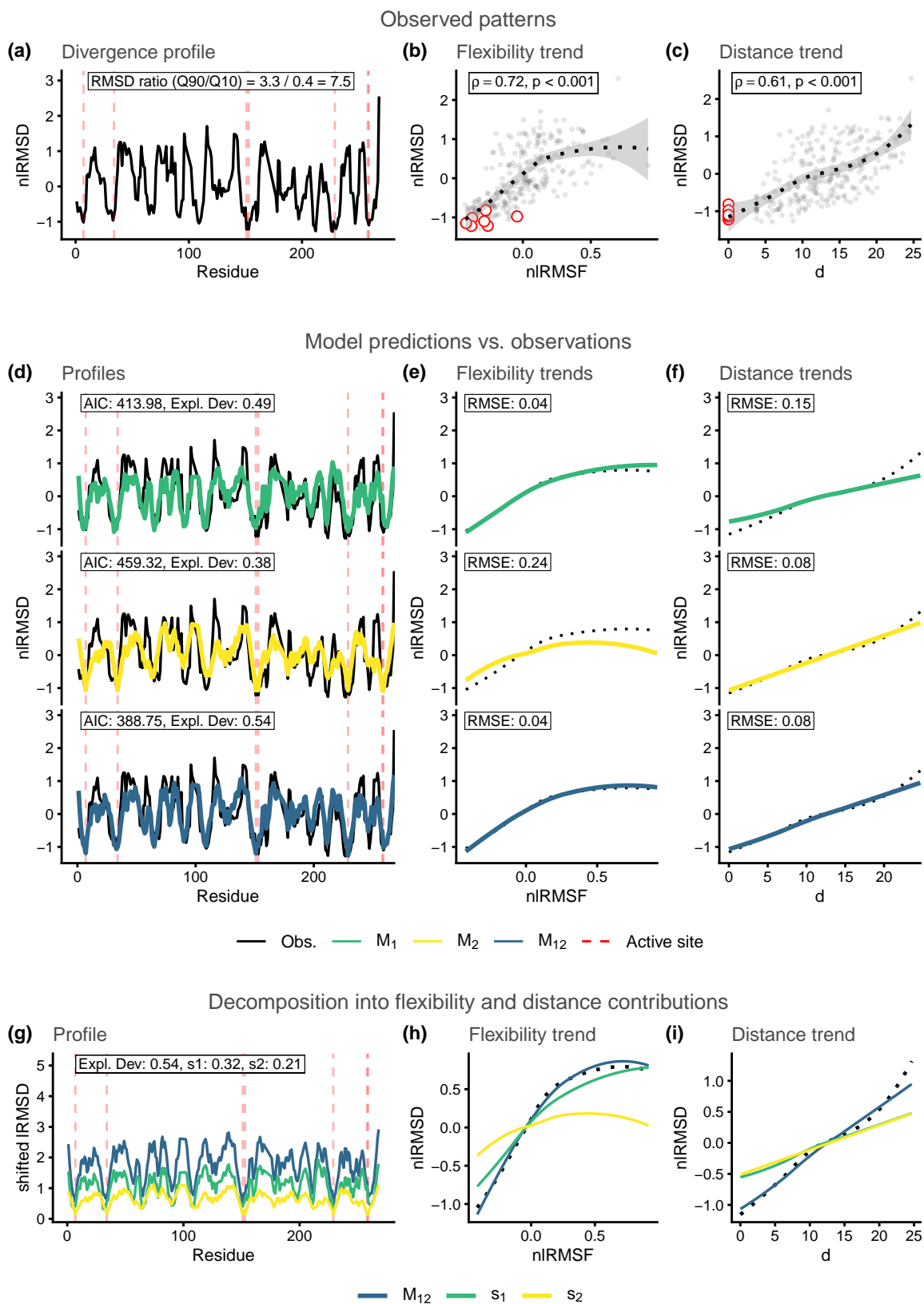


Figure S10: Structural divergence analysis for enzyme family MCSA ID: 160. Reference protein PDB ID: 1ako_A.

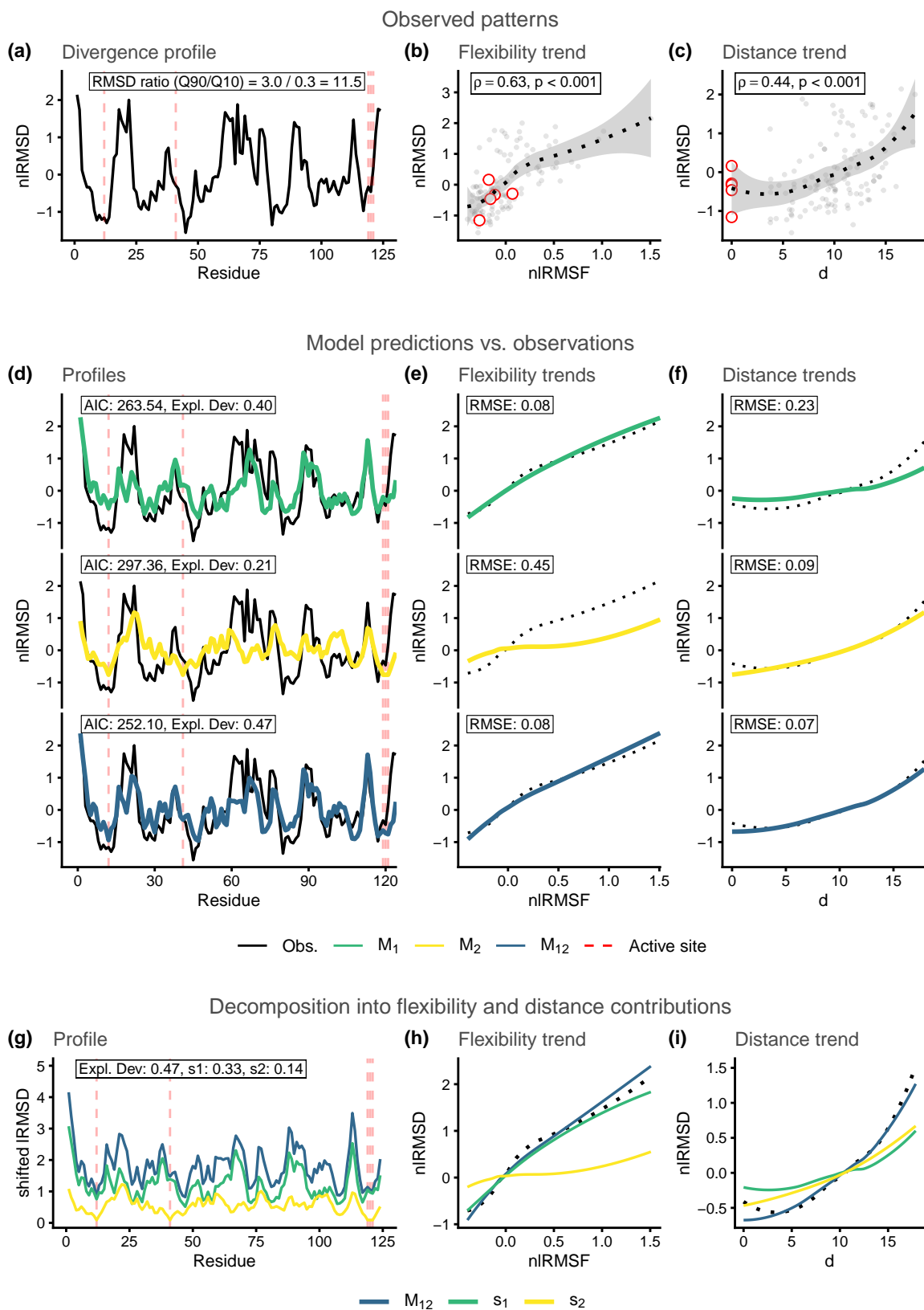


Figure S11: Structural divergence analysis for enzyme family MCSA ID: 164. Reference protein PDB ID: 1ruv_A.

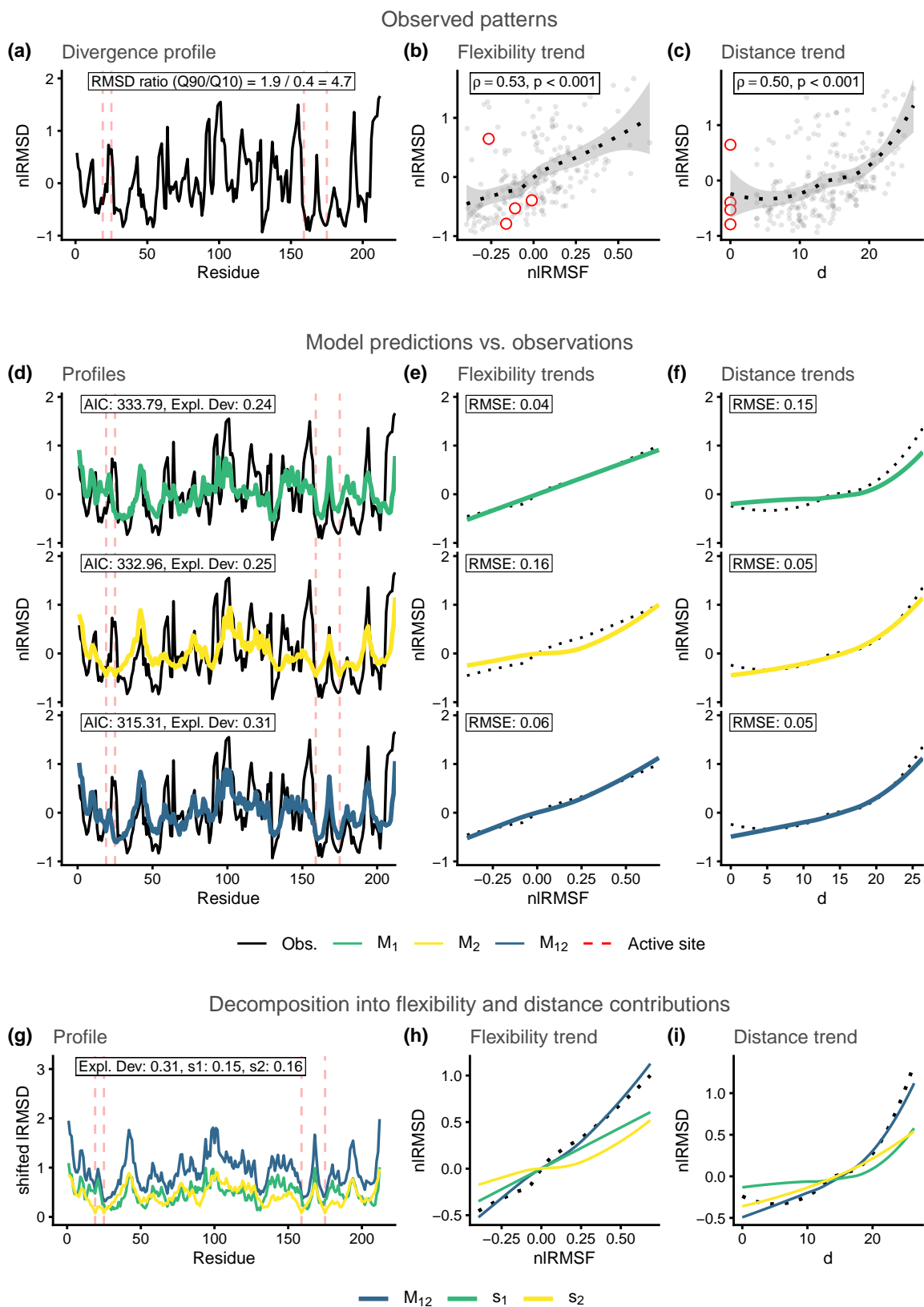


Figure S12: Structural divergence analysis for enzyme family MCSA ID: 174. Reference protein PDB ID: 9pap_A.

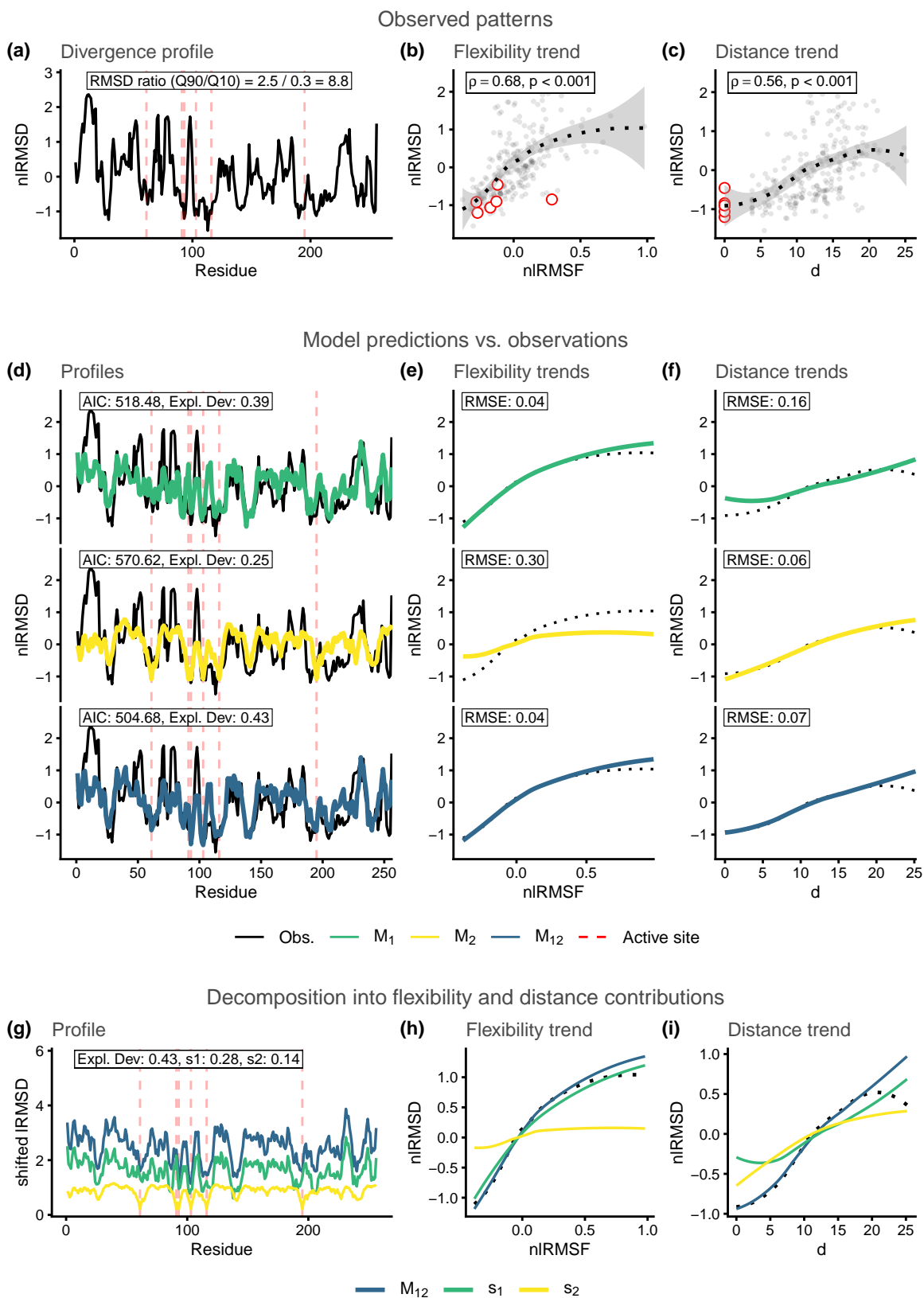


Figure S13: Structural divergence analysis for enzyme family MCSA ID: 216. Reference protein PDB ID: 1ca2_A.

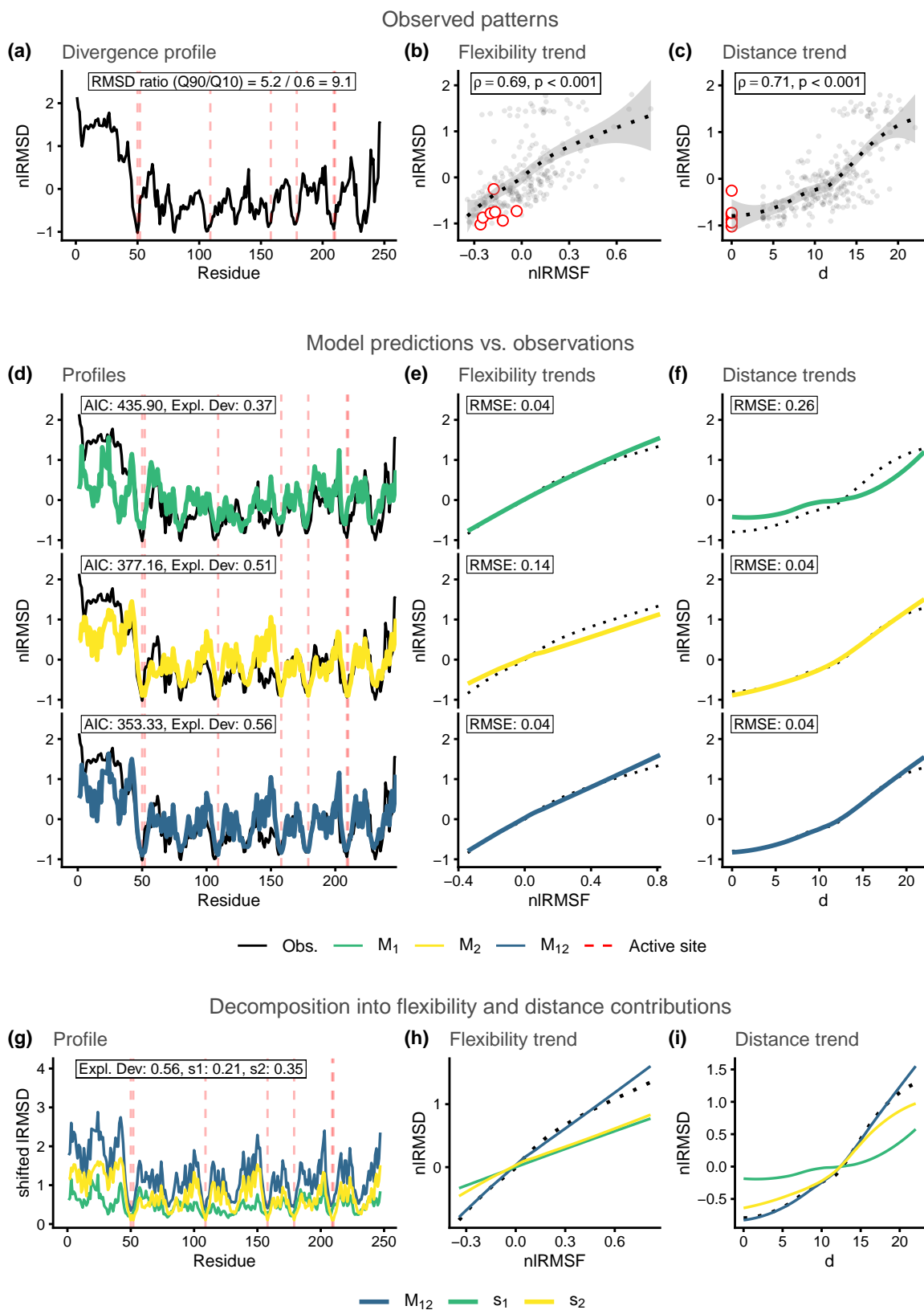


Figure S14: Structural divergence analysis for enzyme family MCSA ID: 252. Reference protein PDB ID: ligs_A.

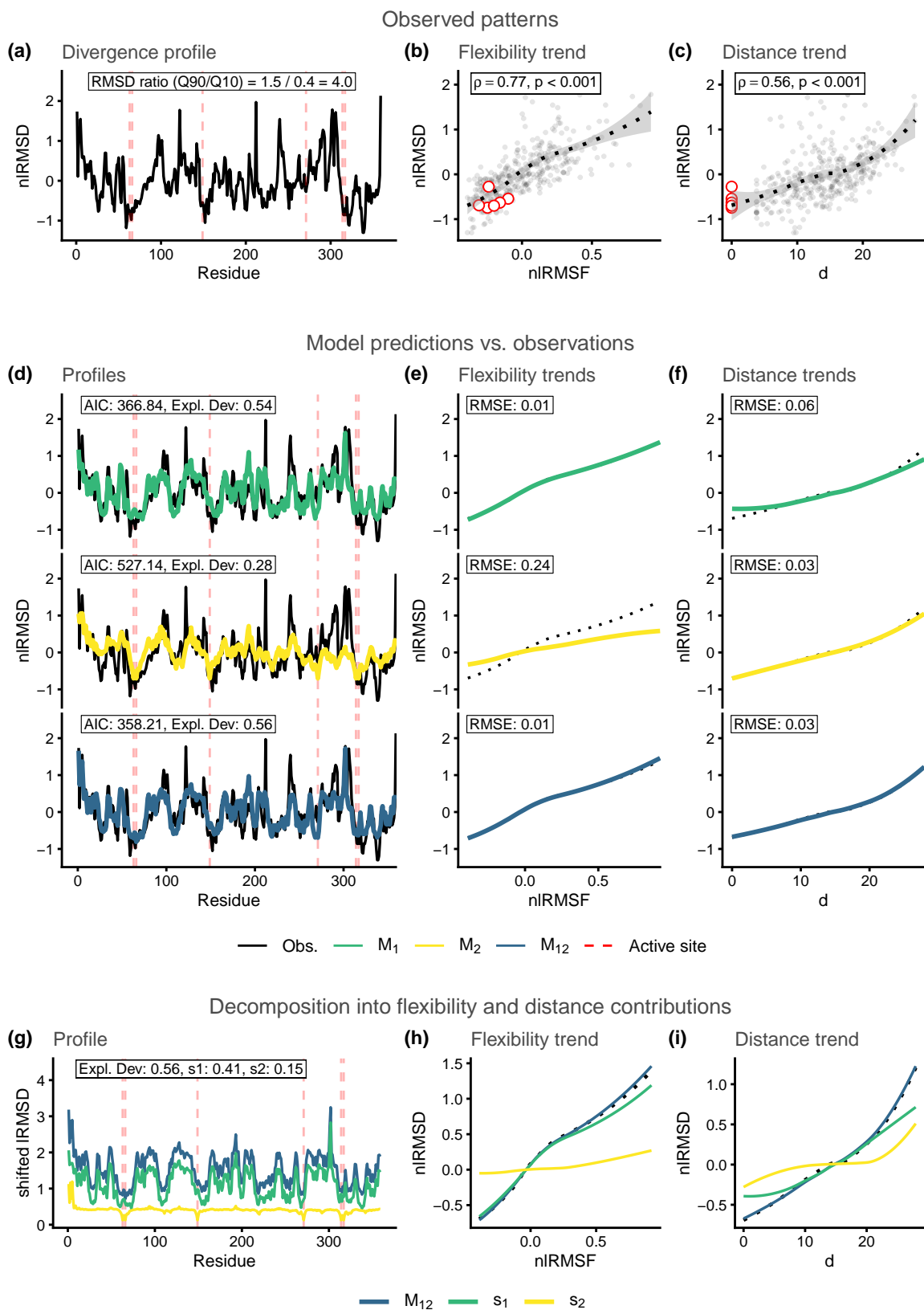


Figure S15: Structural divergence analysis for enzyme family MCSA ID: 257. Reference protein PDB ID: 1xx2_A.

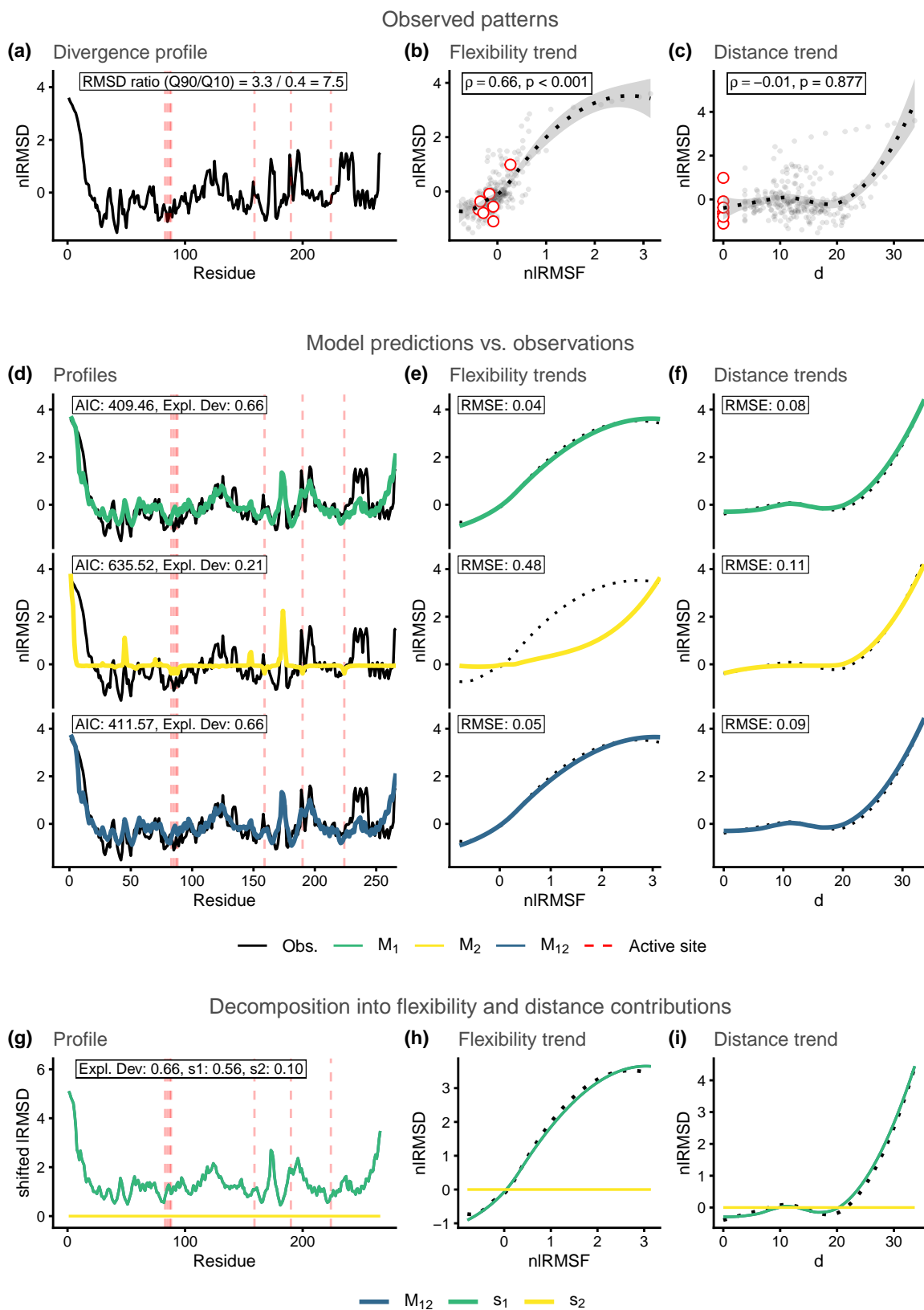


Figure S16: Structural divergence analysis for enzyme family MCSA ID: 258. Reference protein PDB ID: 1sml_A.

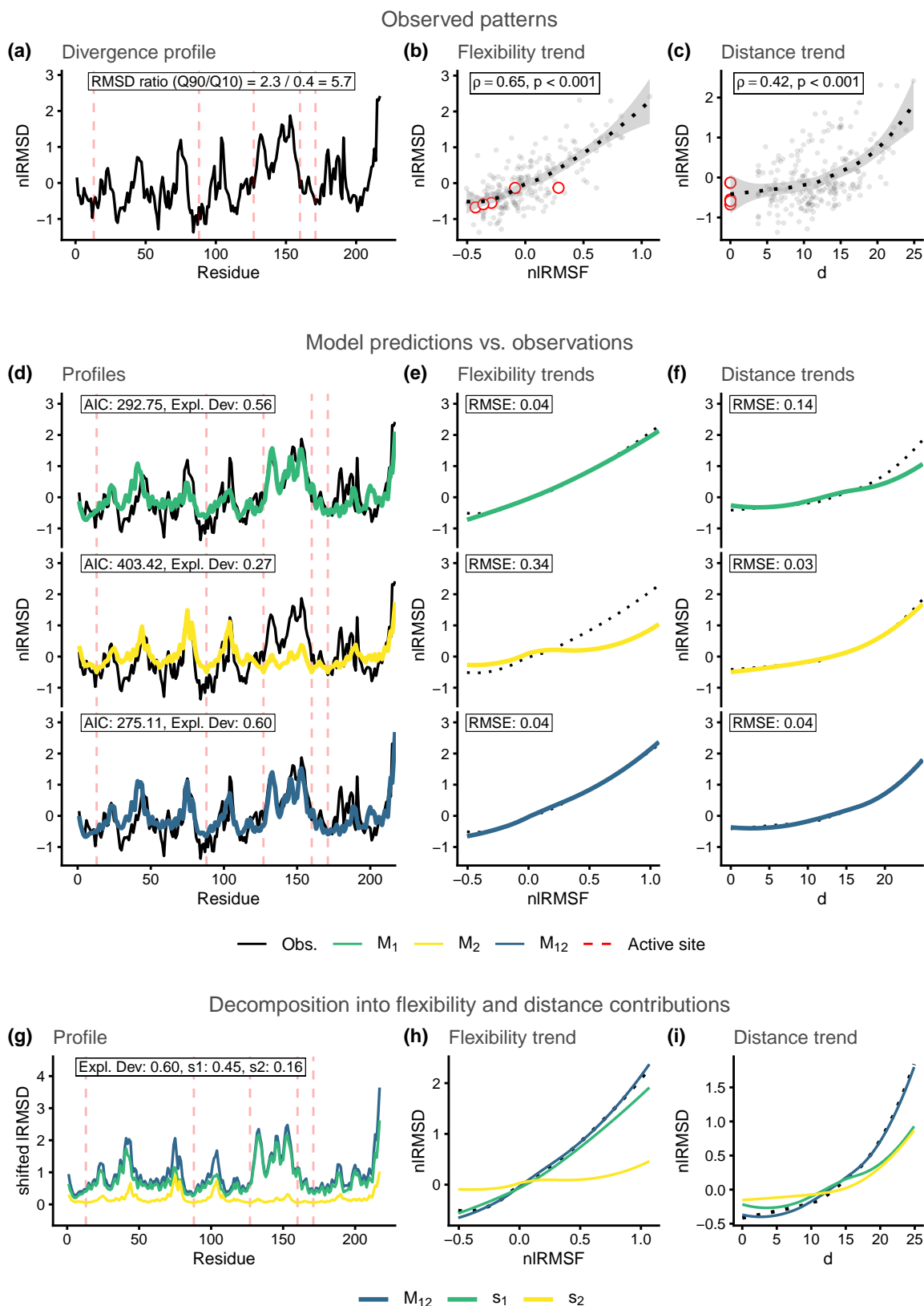


Figure S17: Structural divergence analysis for enzyme family MCSA ID: 290. Reference protein PDB ID: 1zio_A.

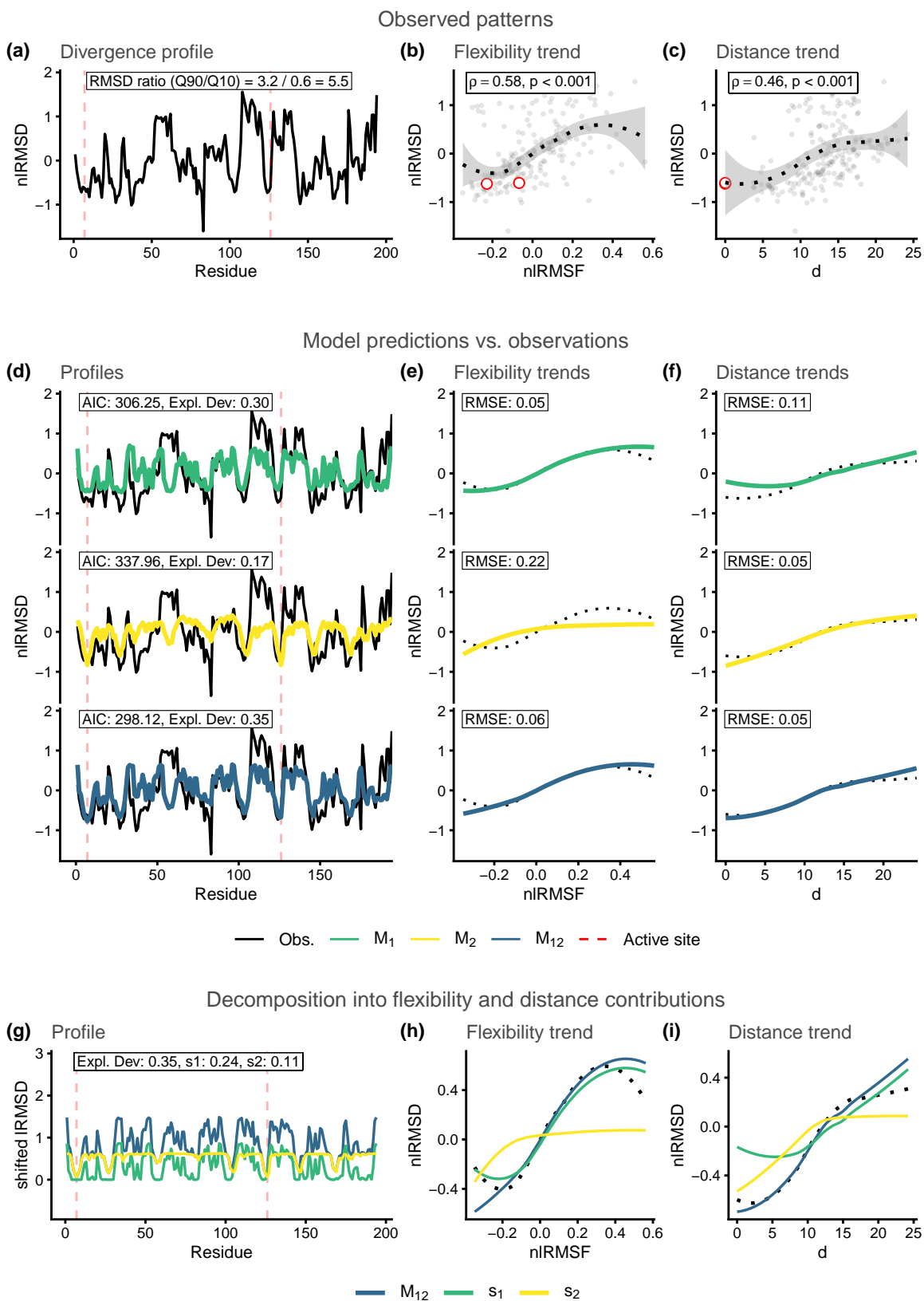


Figure S18: Structural divergence analysis for enzyme family MCSA ID: 328. Reference protein PDB ID: 1lbm_A.

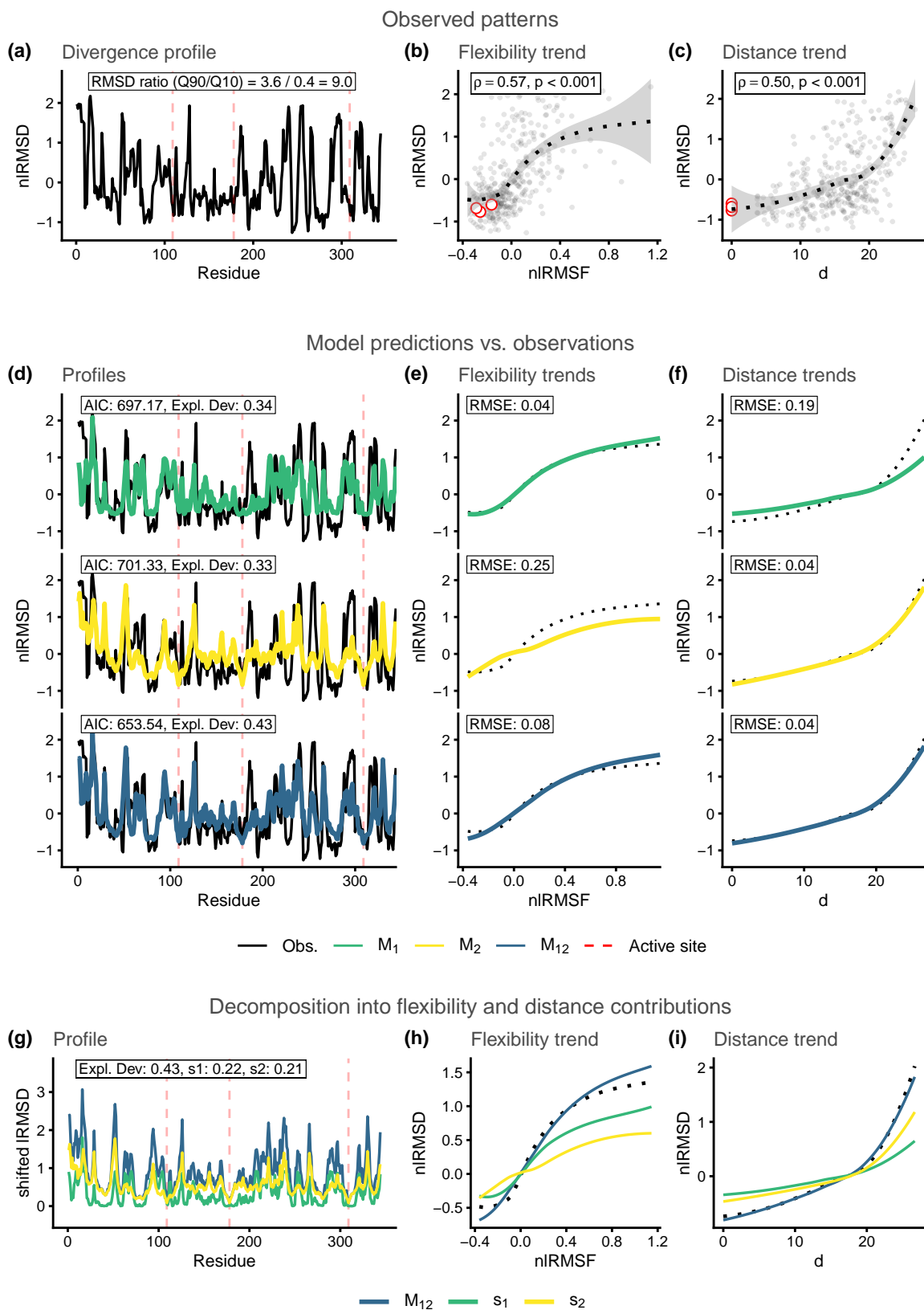


Figure S19: Structural divergence analysis for enzyme family MCSA ID: 351. Reference protein PDB ID: 1snz_A.

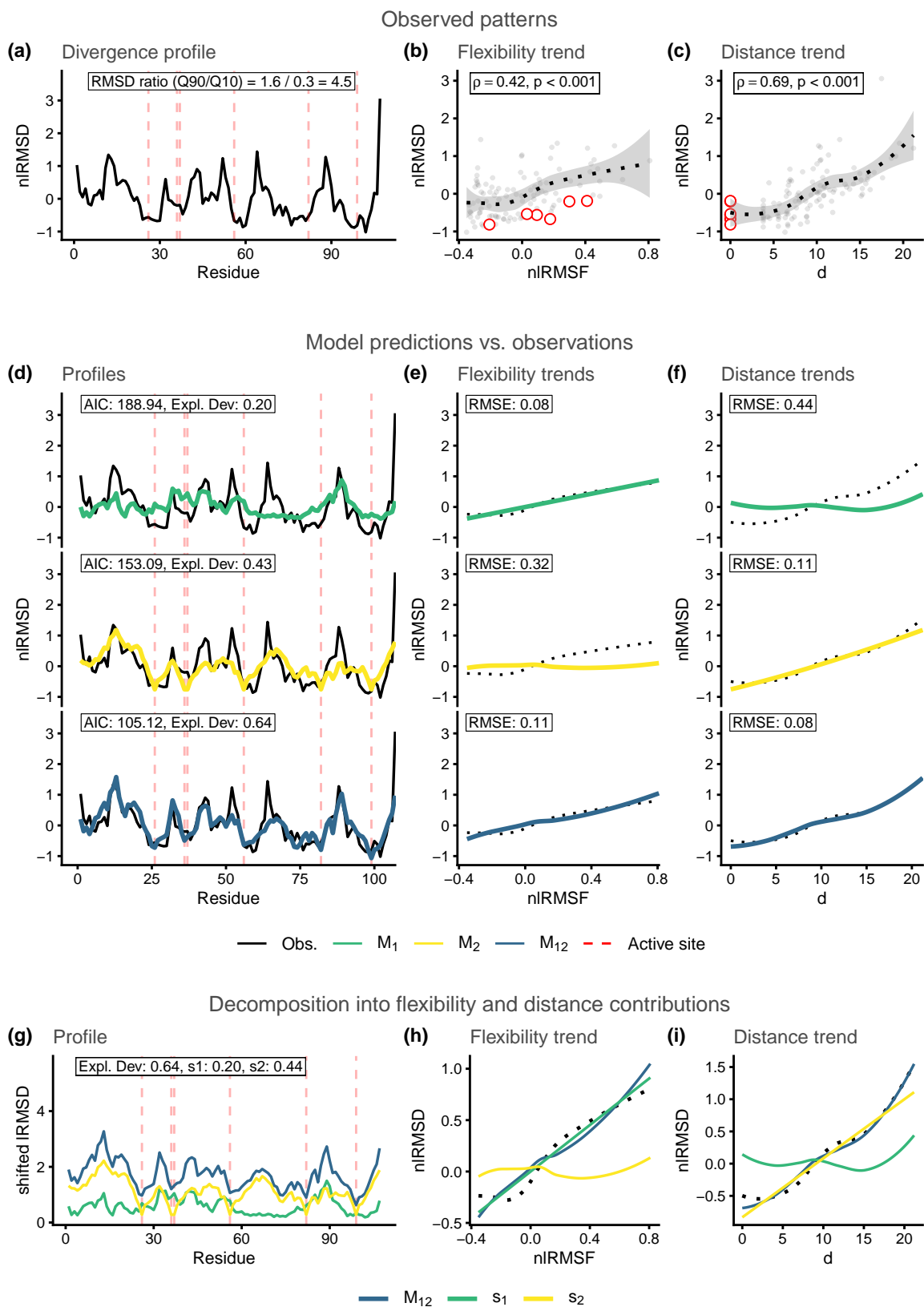


Figure S20: Structural divergence analysis for enzyme family MCSA ID: 362. Reference protein PDB ID: 1d6o_A.

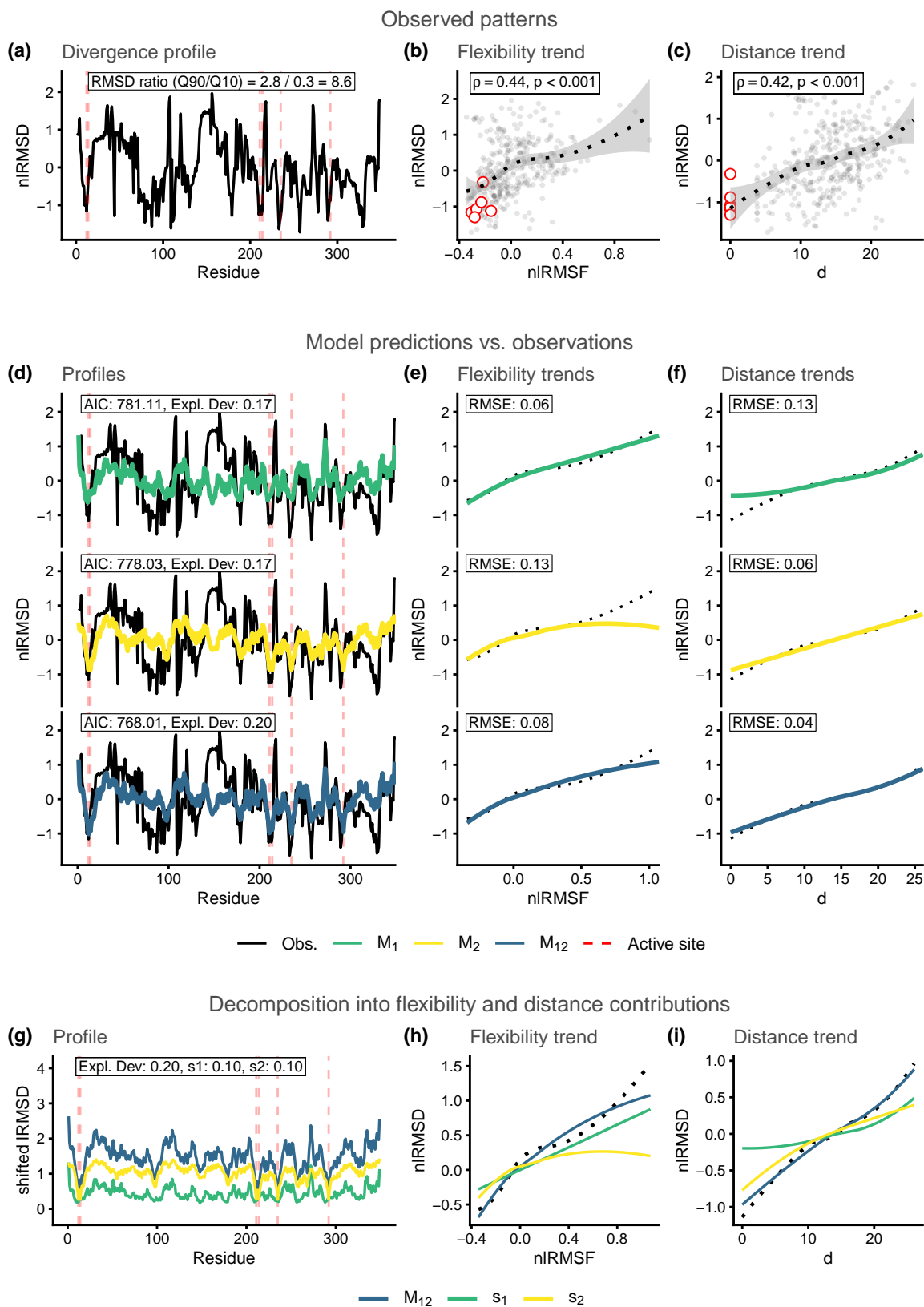


Figure S21: Structural divergence analysis for enzyme family MCSA ID: 376. Reference protein PDB ID: 1a4l_A.

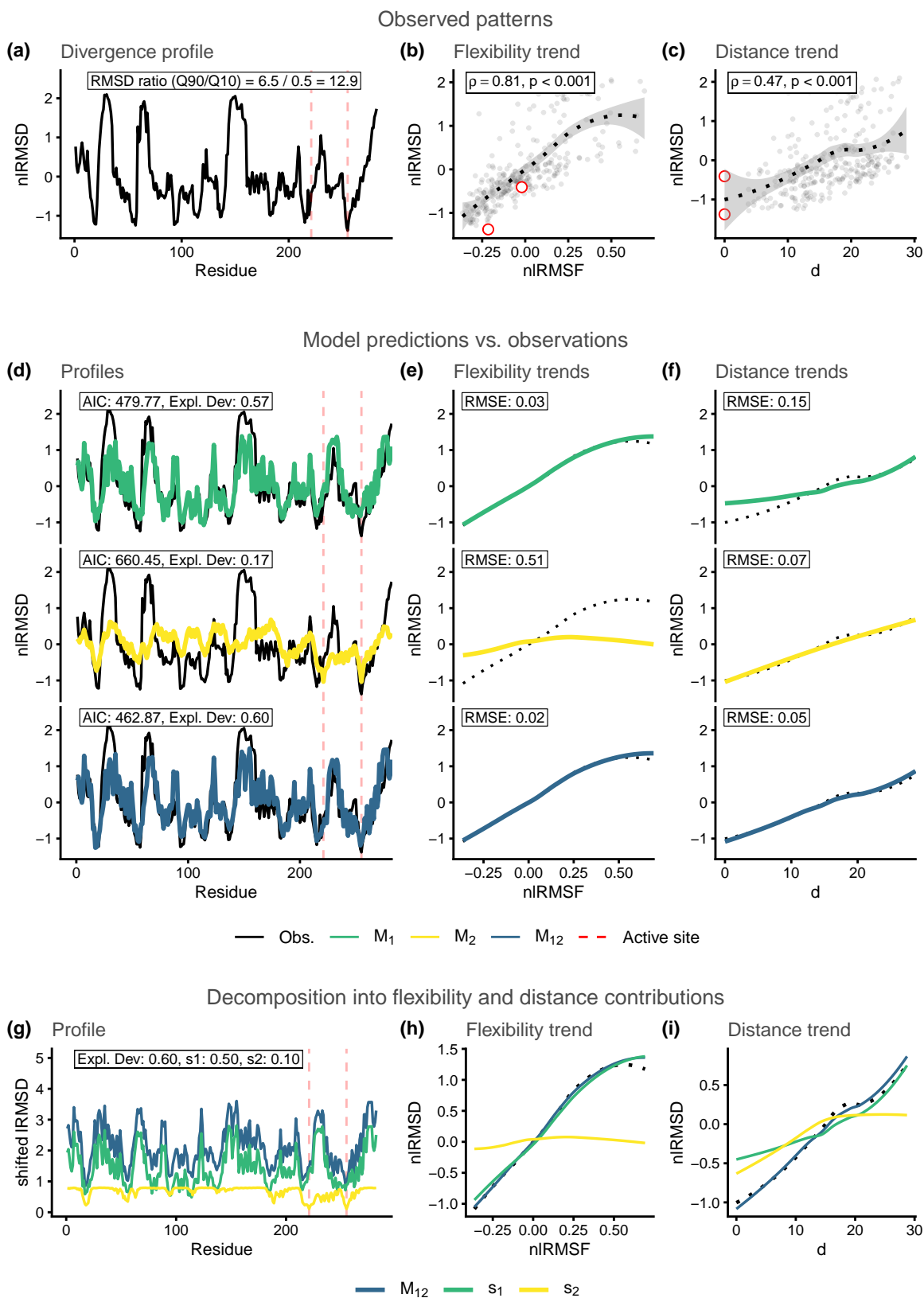


Figure S22: Structural divergence analysis for enzyme family MCSA ID: 394. Reference protein PDB ID: 1aj0_A.

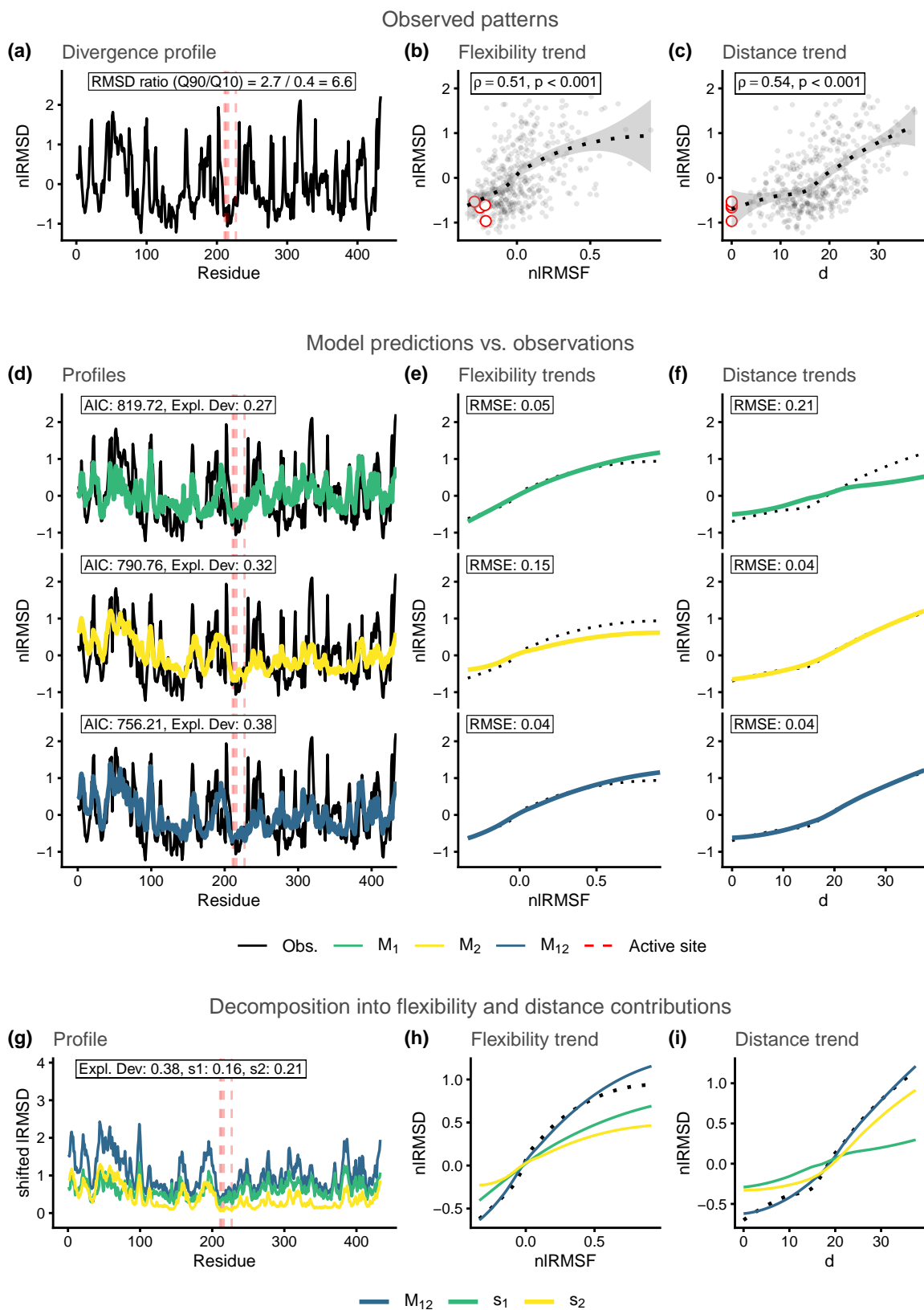


Figure S23: Structural divergence analysis for enzyme family MCSA ID: 444. Reference protein PDB ID: 1cel_A.

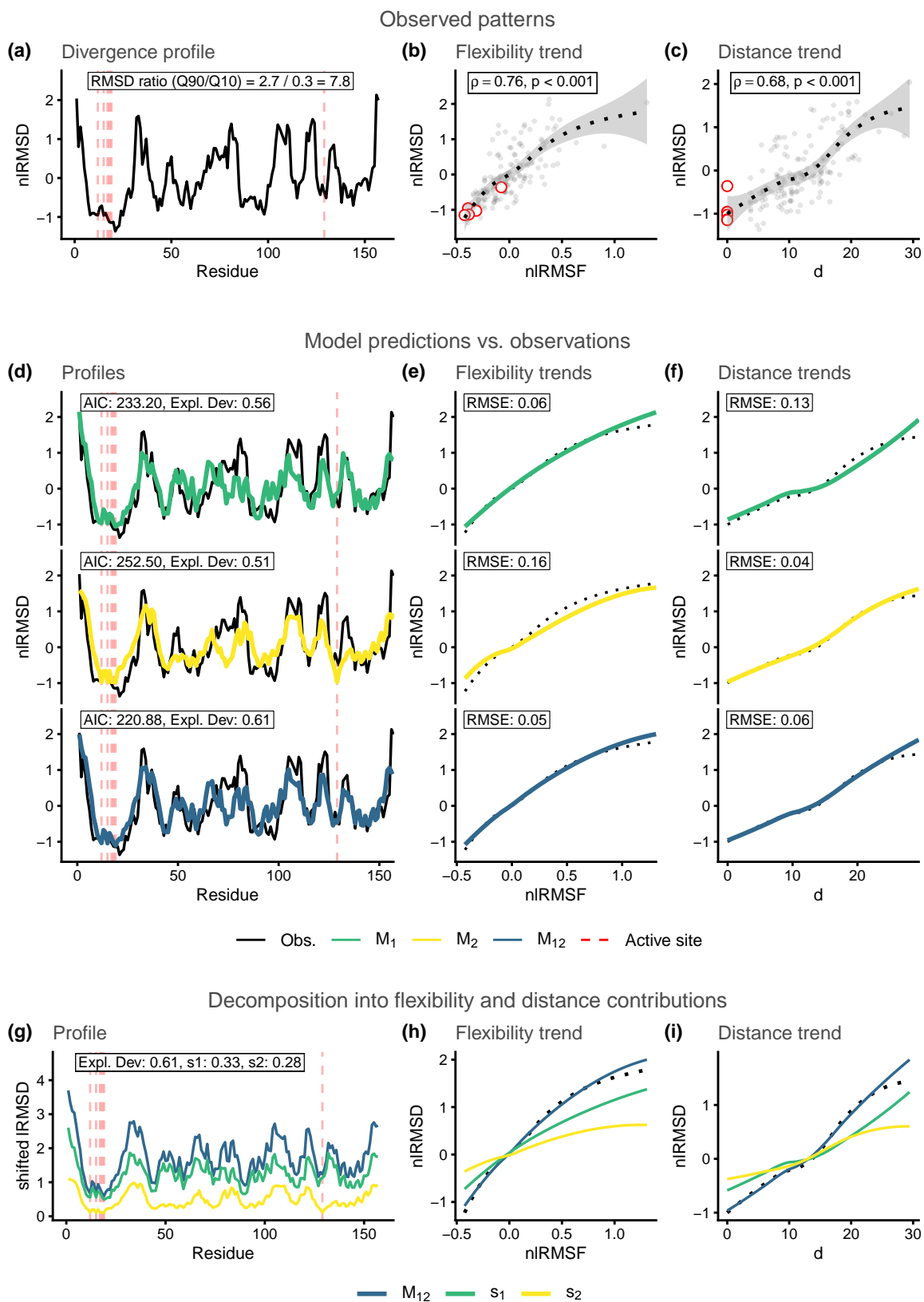


Figure S24: Structural divergence analysis for enzyme family MCSA ID: 462. Reference protein PDB ID: 1pnt_A.

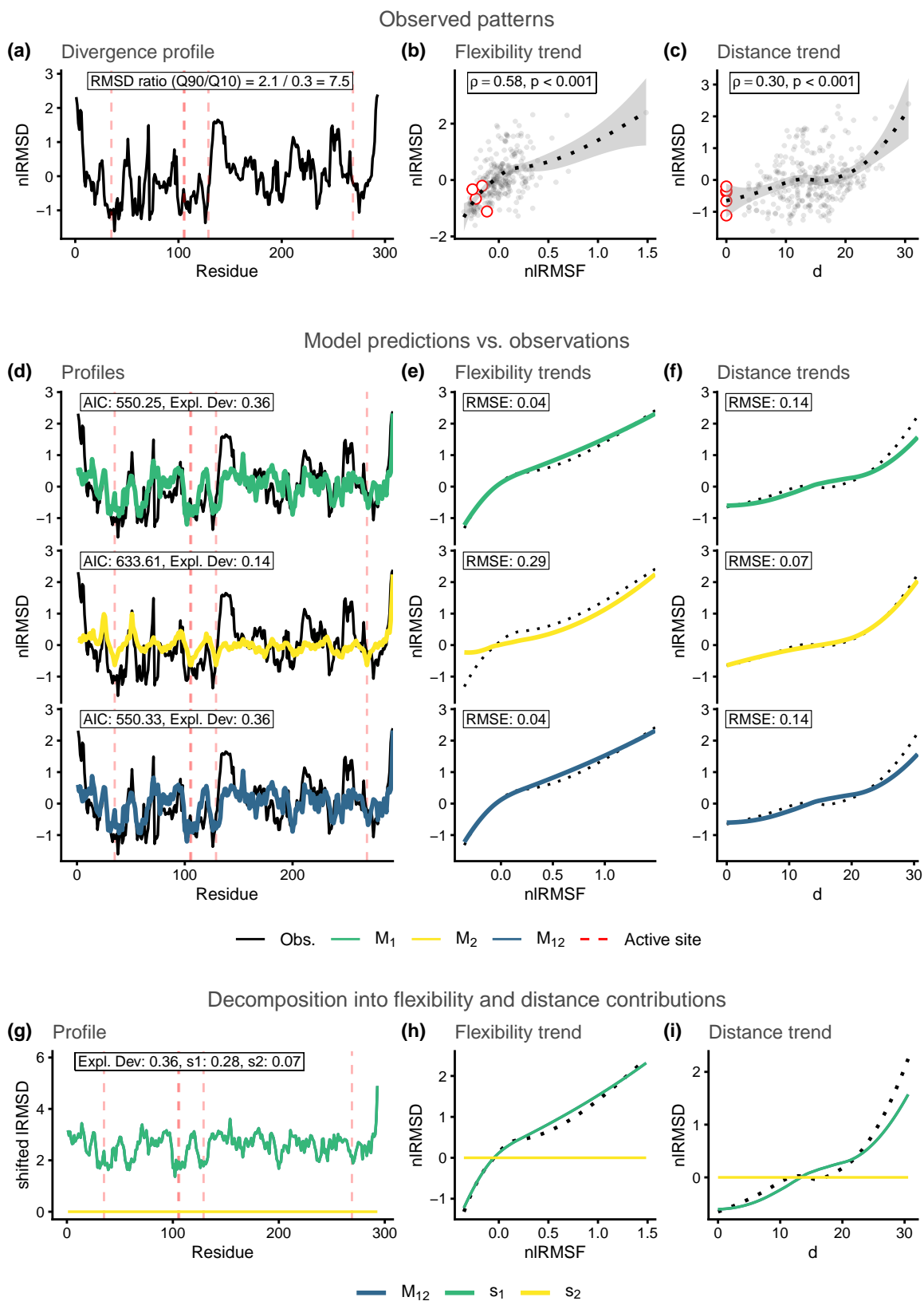


Figure S25: Structural divergence analysis for enzyme family MCSA ID: 467. Reference protein PDB ID: 1cv2_A.

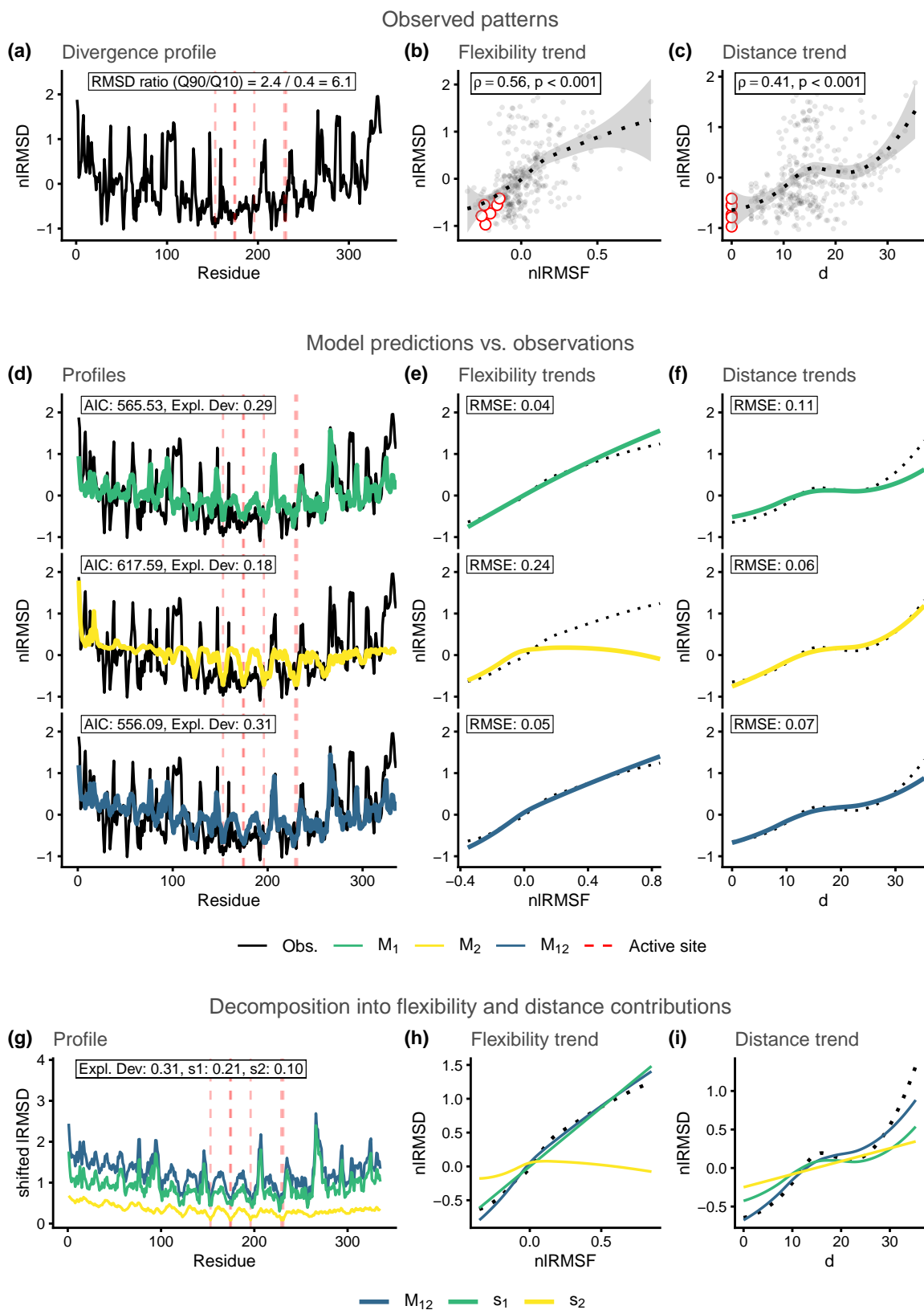


Figure S26: Structural divergence analysis for enzyme family MCSA ID: 480. Reference protein PDB ID: 1czf_A.

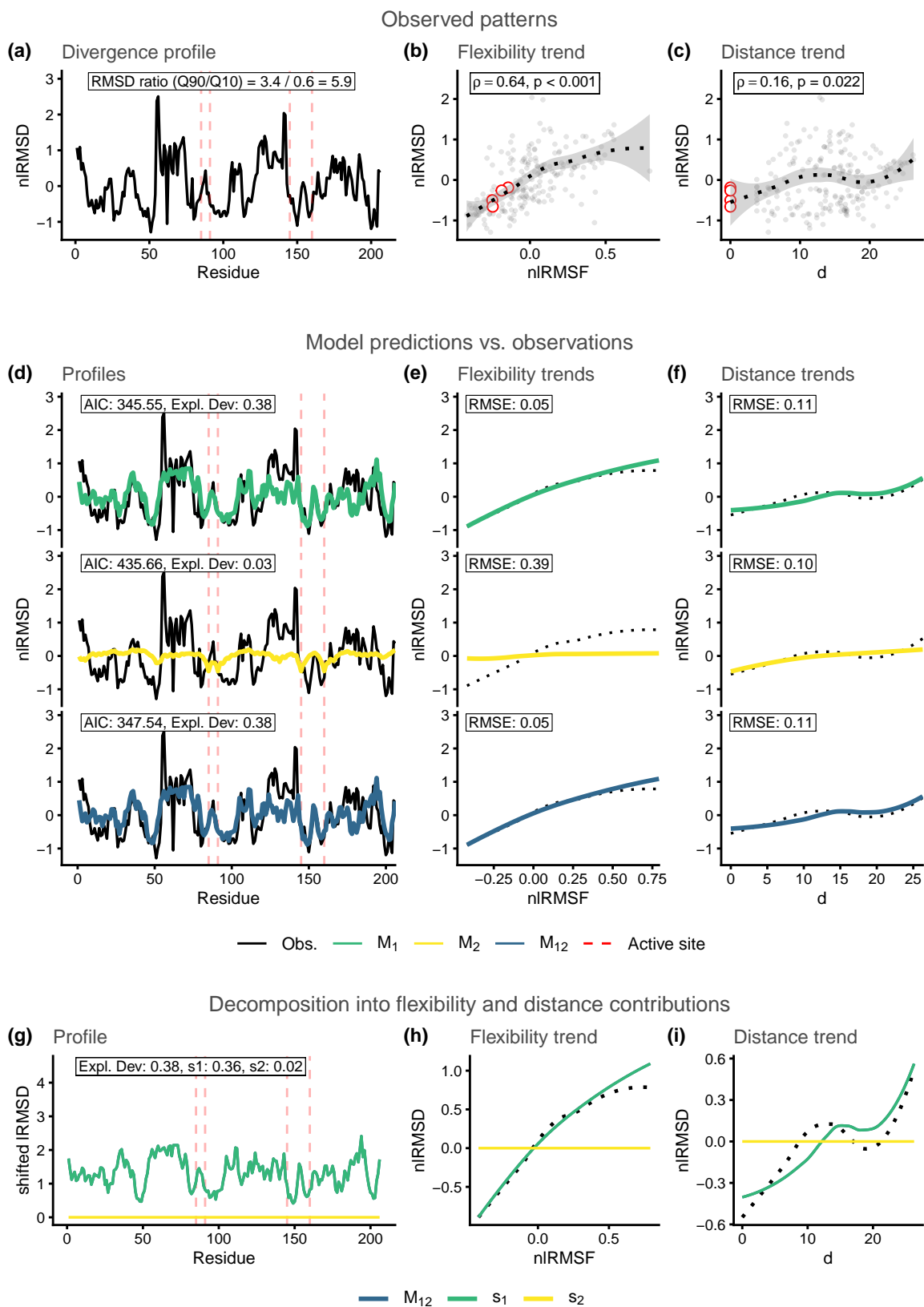


Figure S27: Structural divergence analysis for enzyme family MCSA ID: 597. Reference protein PDB ID: 1uch_A.

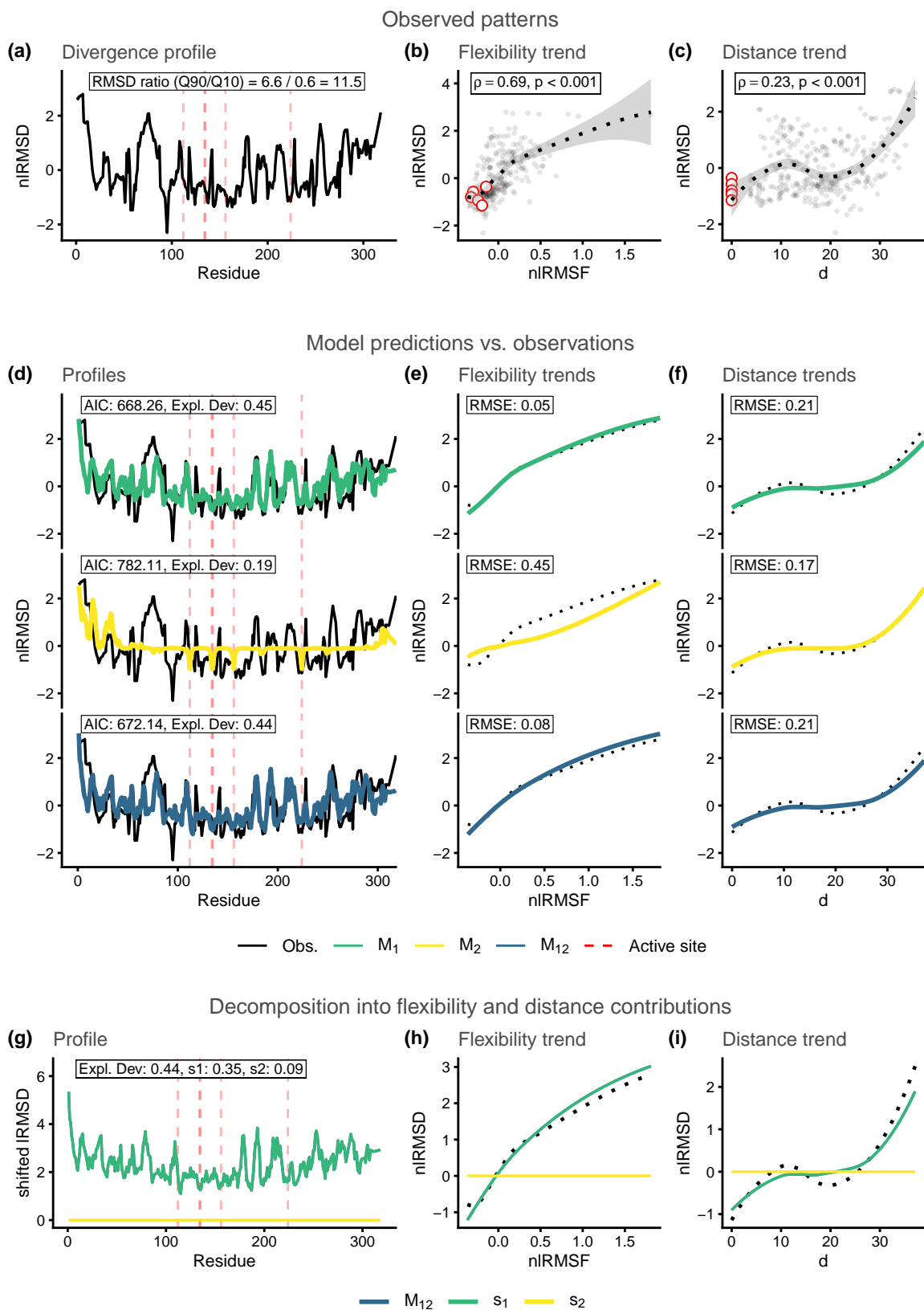


Figure S28: Structural divergence analysis for enzyme family MCSA ID: 681. Reference protein PDB ID: 1gq8_A.

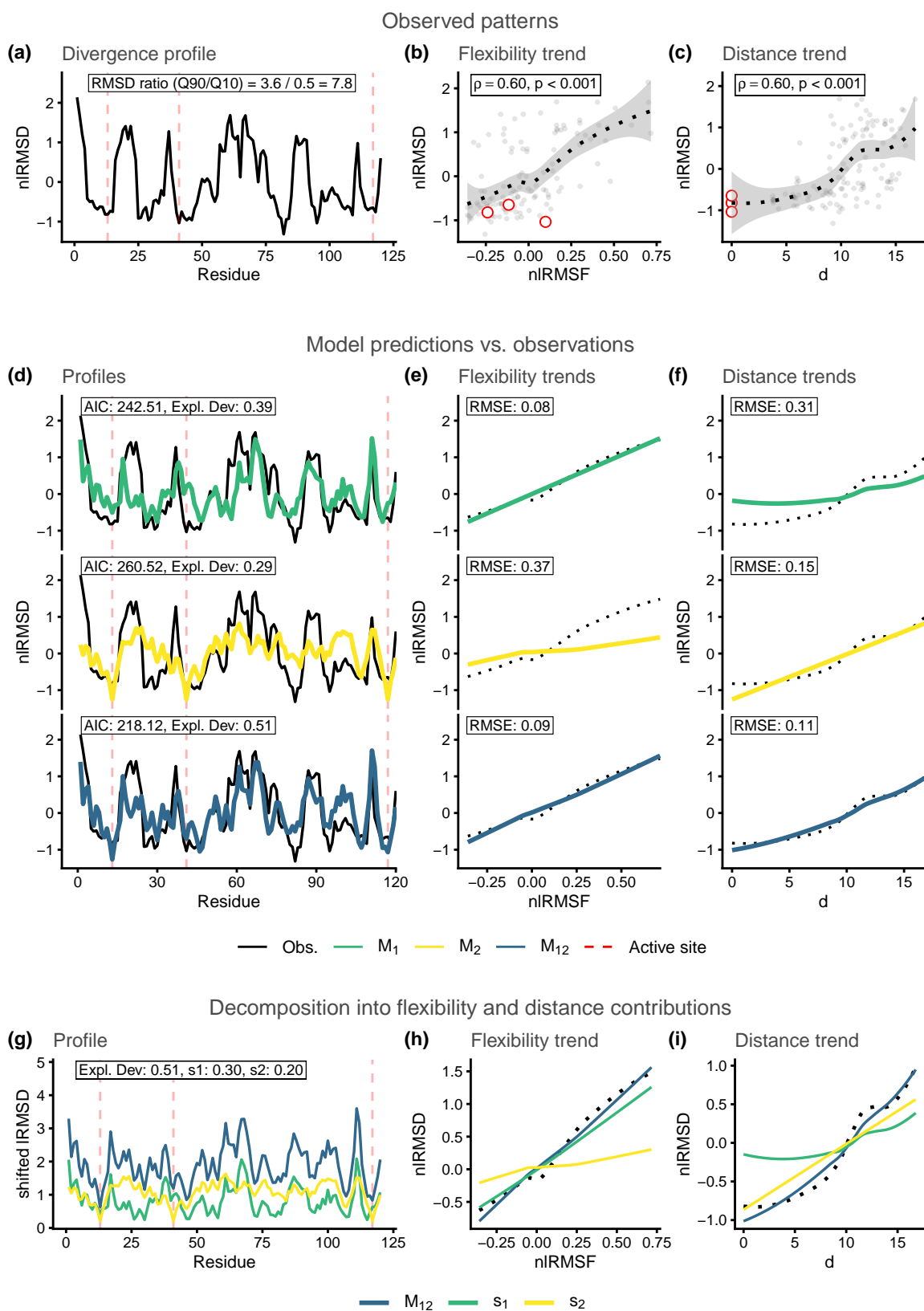


Figure S29: Structural divergence analysis for enzyme family MCSA ID: 693. Reference protein PDB ID: 2rnf_A.

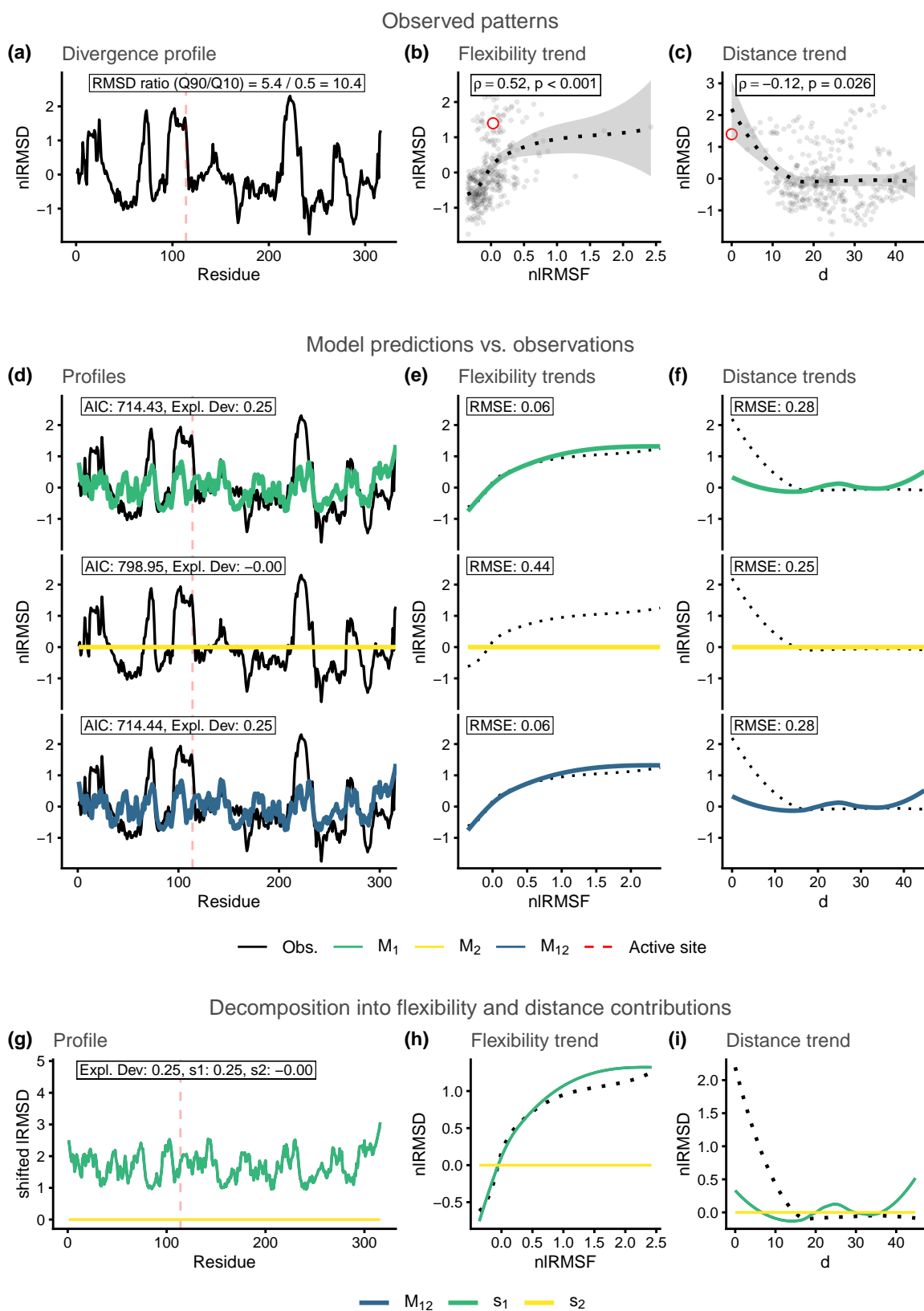


Figure S30: Structural divergence analysis for enzyme family MCSA ID: 749. Reference protein PDB ID: 1nml_A.

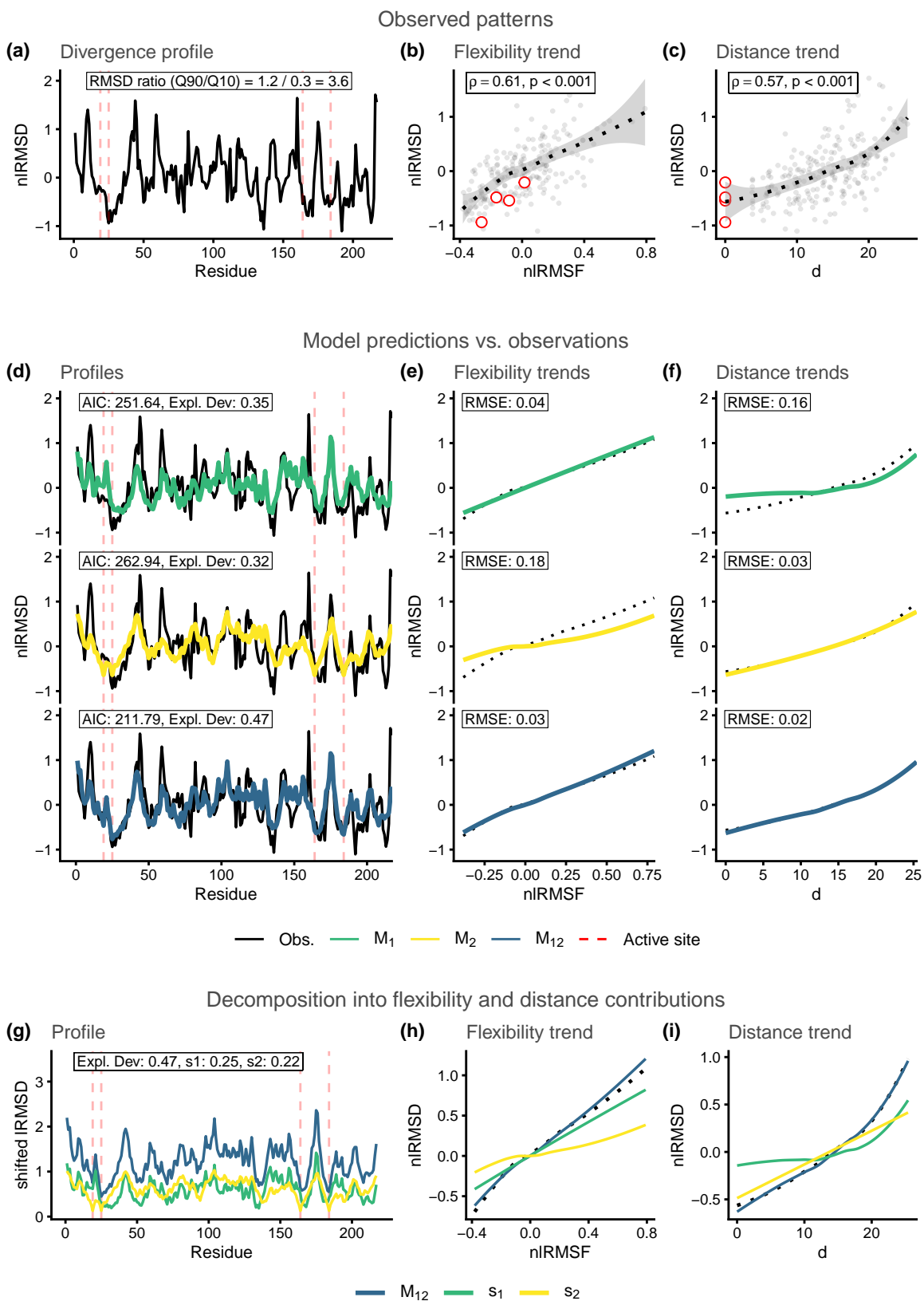


Figure S31: Structural divergence analysis for enzyme family MCSA ID: 814. Reference protein PDB ID: 1glo_A.

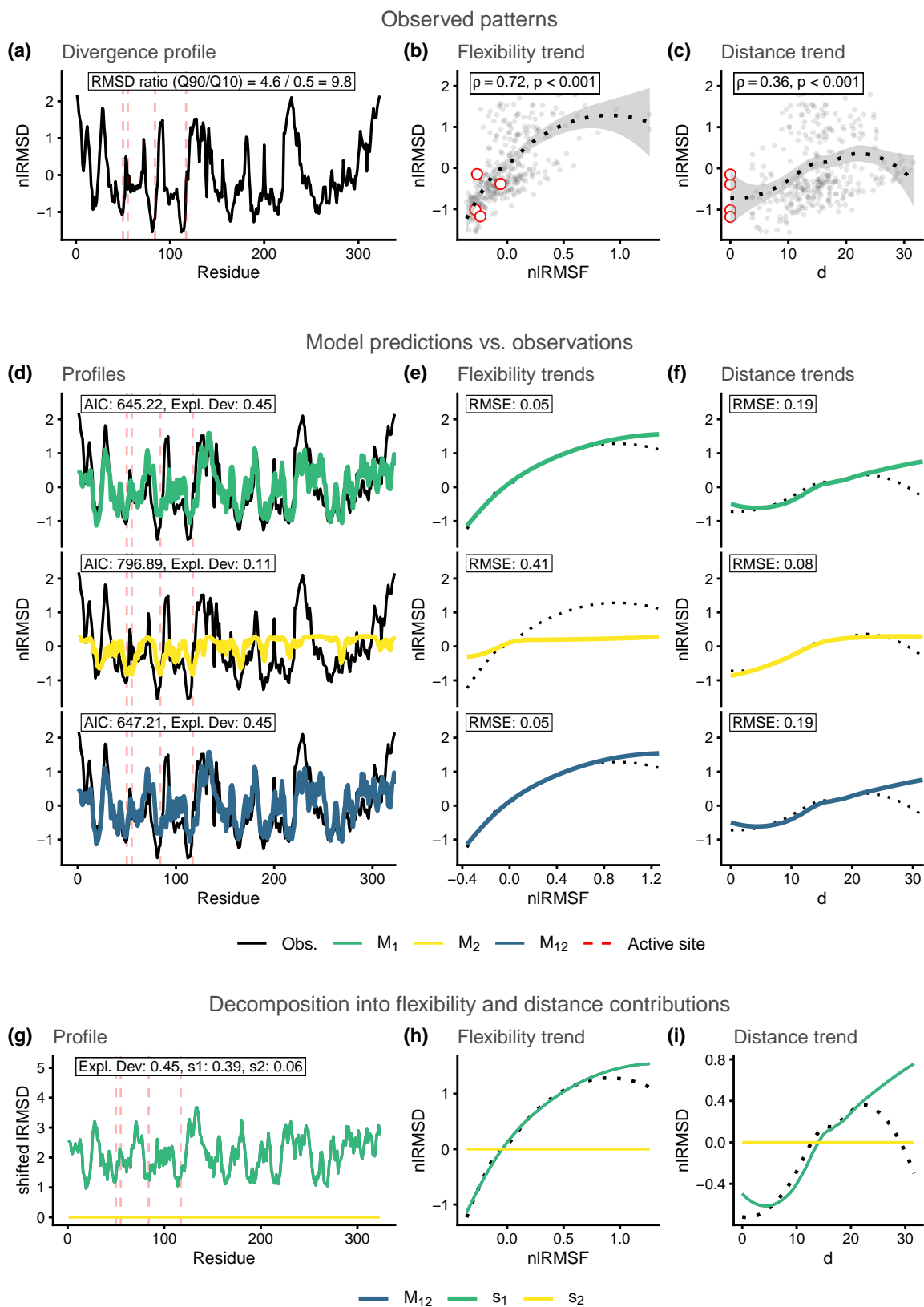


Figure S32: Structural divergence analysis for enzyme family MCSA ID: 858. Reference protein PDB ID: 1mrq_A.

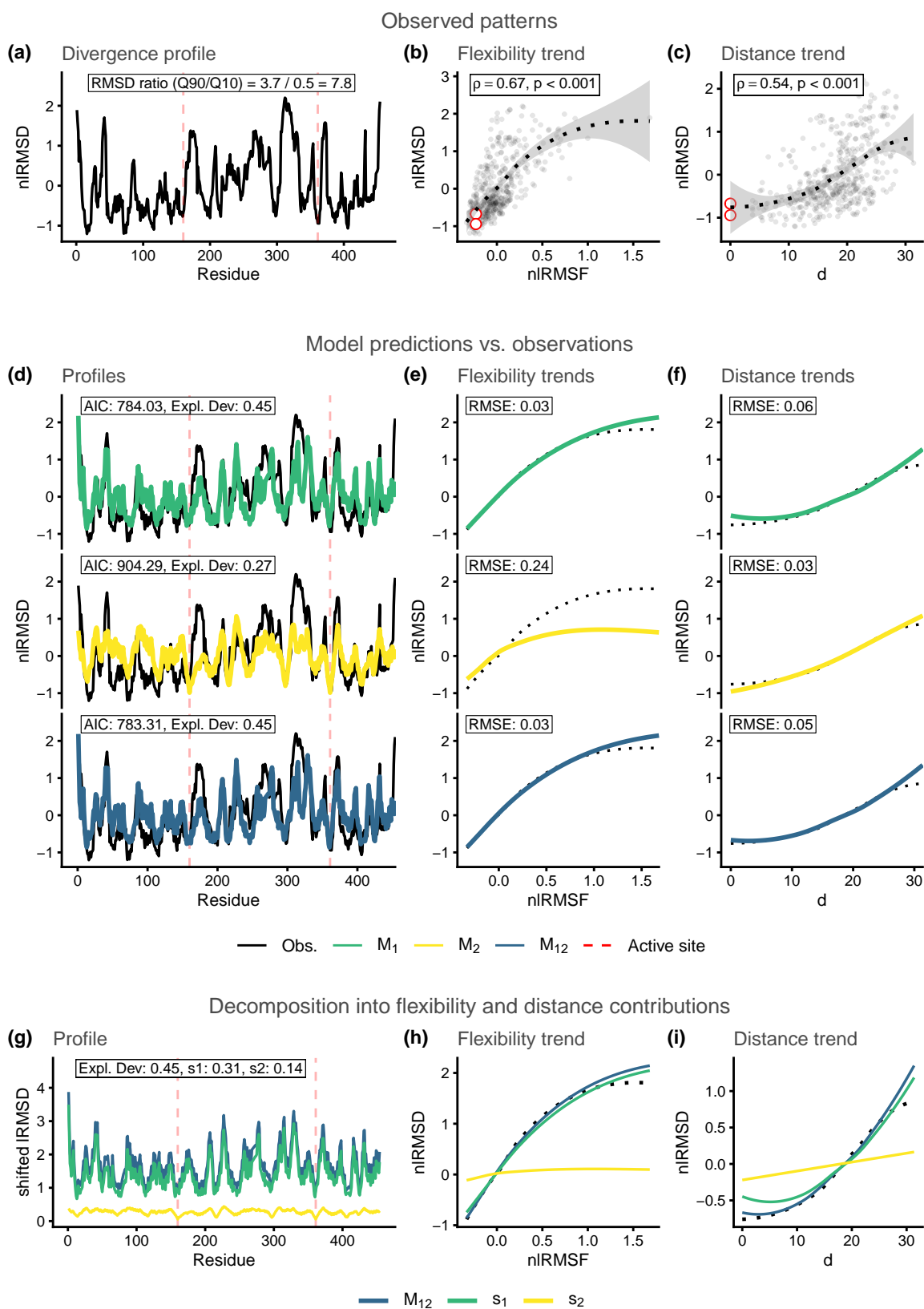


Figure S33: Structural divergence analysis for enzyme family MCSA ID: 877. Reference protein PDB ID: 1pbg_A.

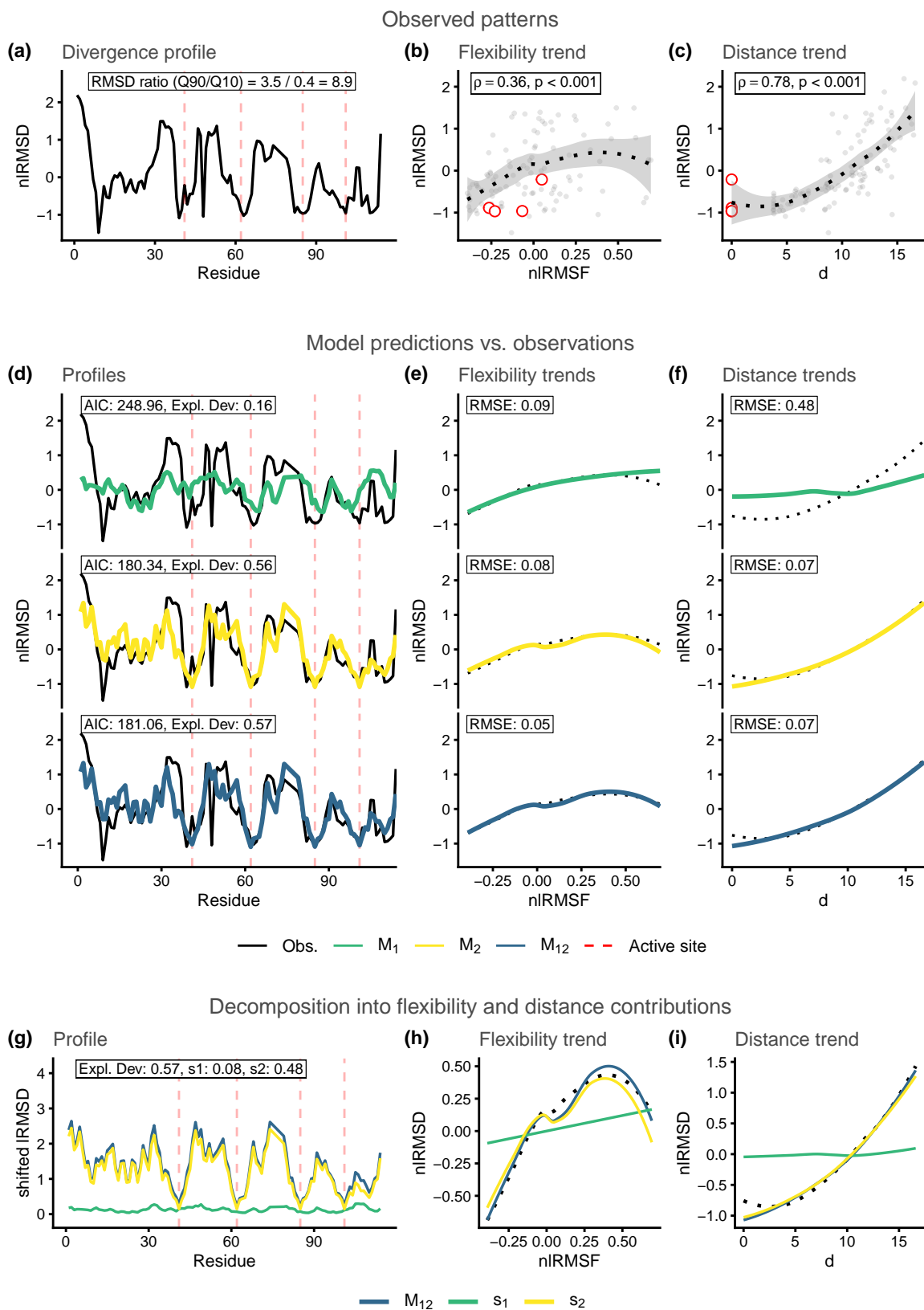


Figure S34: Structural divergence analysis for enzyme family MCSA ID: 908. Reference protein PDB ID: 1rtu_A.

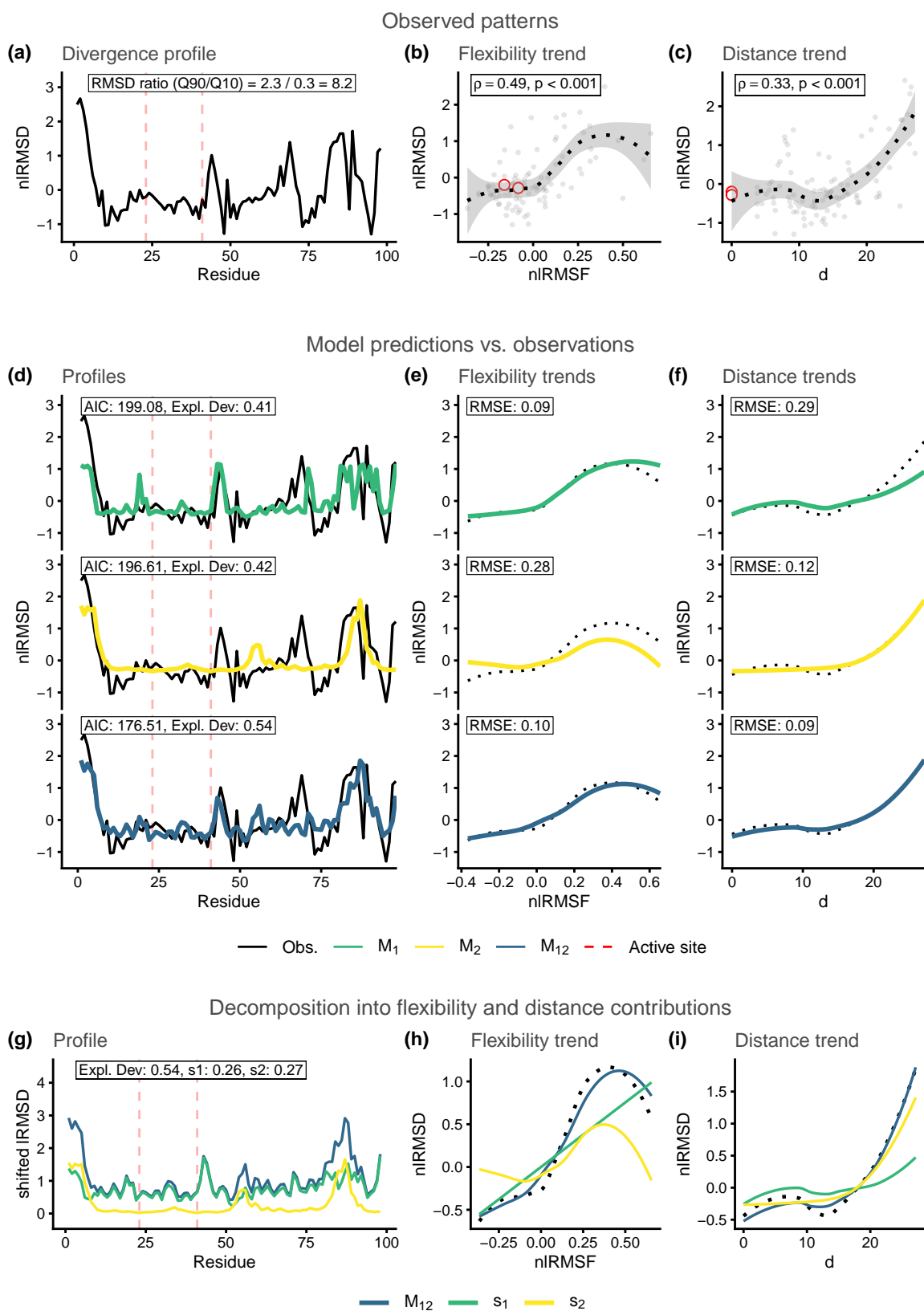


Figure S35: Structural divergence analysis for enzyme family MCSA ID: 923. Reference protein PDB ID: 2acy_A.

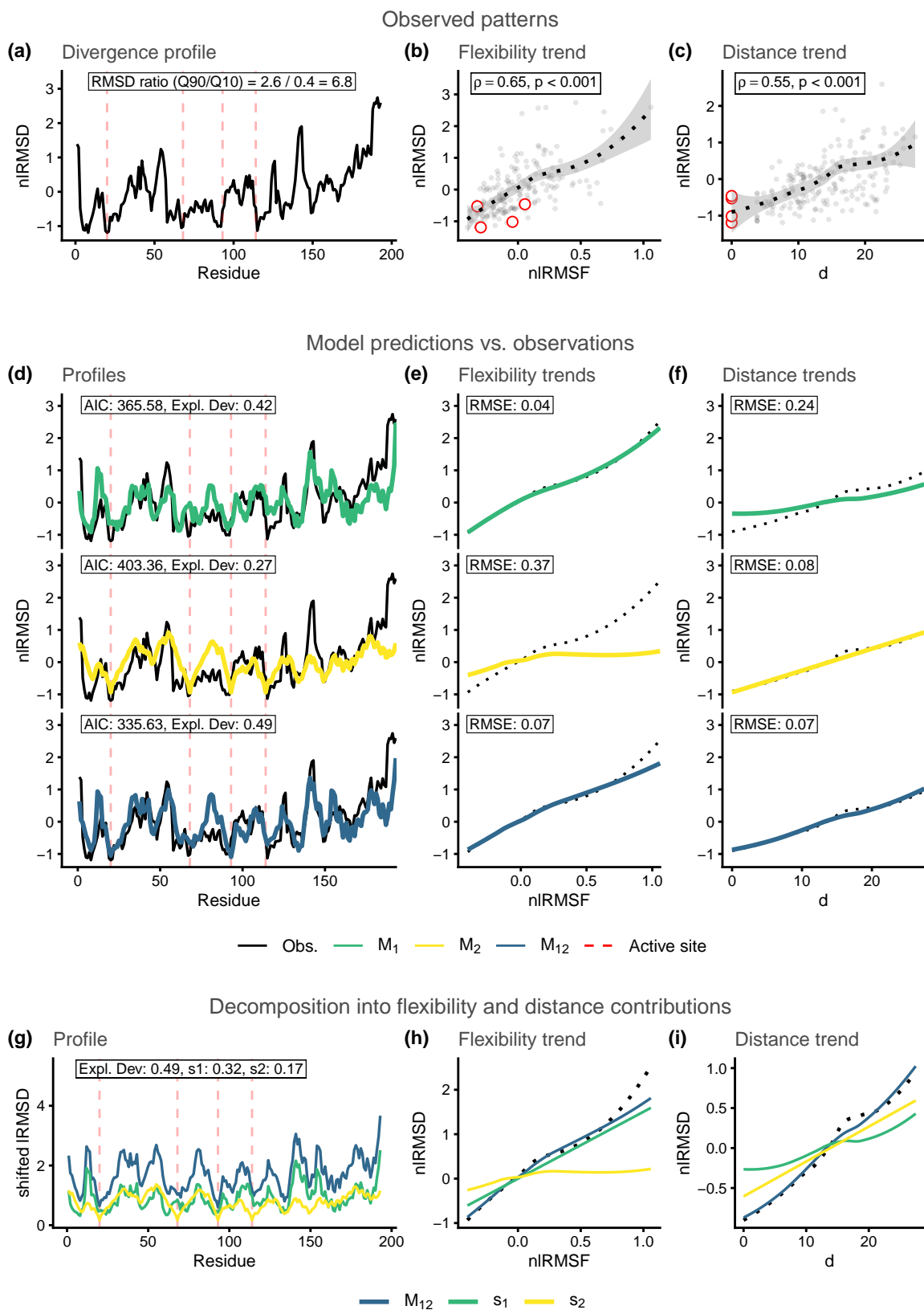


Figure S36: Structural divergence analysis for enzyme family MCSA ID: 931. Reference protein PDB ID: 2pth_A.