

On the variation of structural divergence among residues in enzyme evolution — Supplement

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1. Dataset

Table S1: Dataset entries and reference protein

M-CSA	PDB	Name	Source	Family
2	1blt_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	1sm1_A	Metallo-beta-lactamase L1 type 3	Stenotrophomonas maltophilia	Metallo-beta-lactamase superfamily
290	1zio_A	Adenylate kinase	Geobacillus stearothermophilus	Adenylate kinase family
328	1lbt_A	N-(5'	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	1gg8_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 sphaerogenes	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

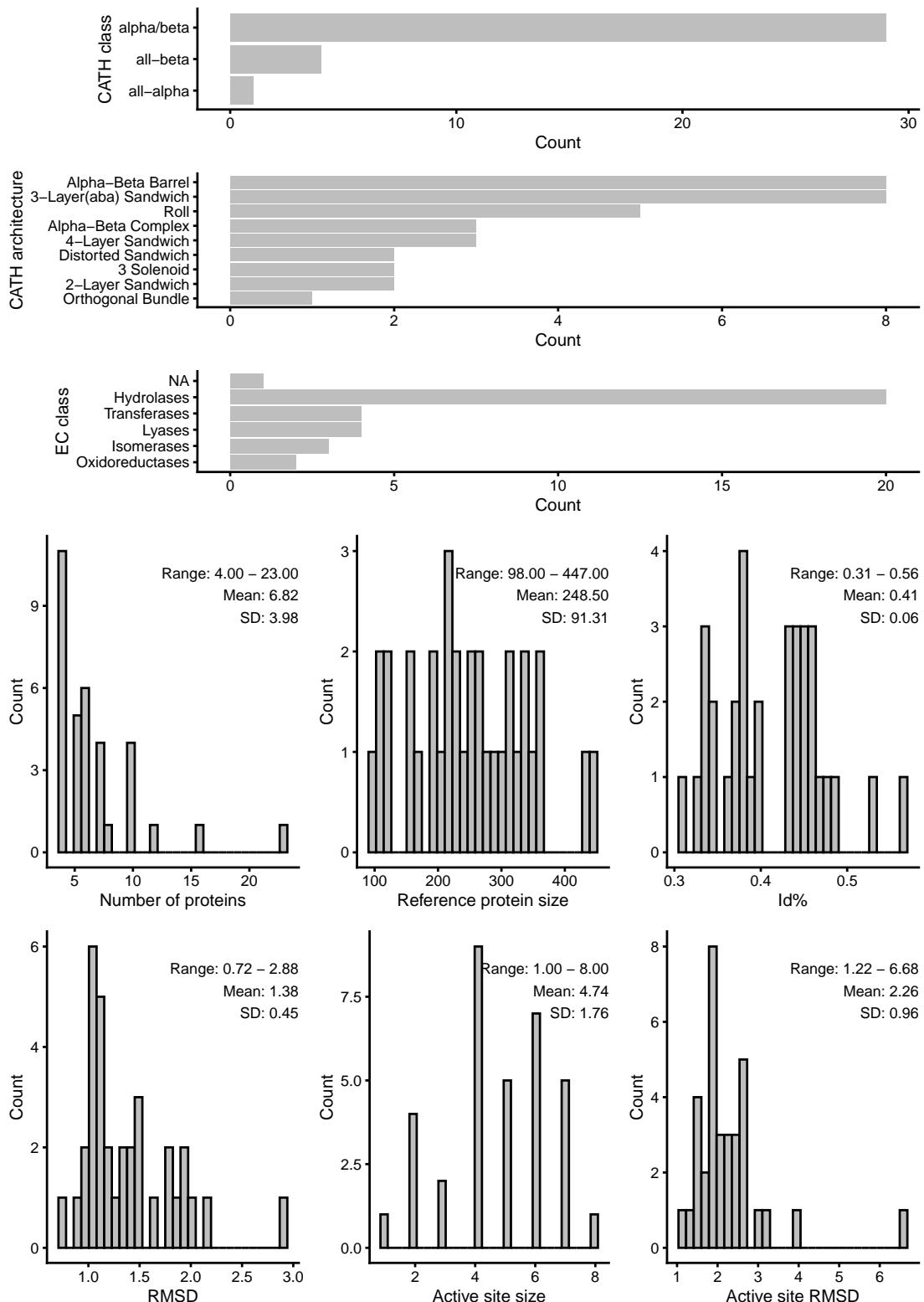


Figure S1: Distribution of properties of dataset families.

2. Correlation between flexibility and distance

The following figure shows the distribution of spearman correlations between flexibility (nIRMSF) 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).

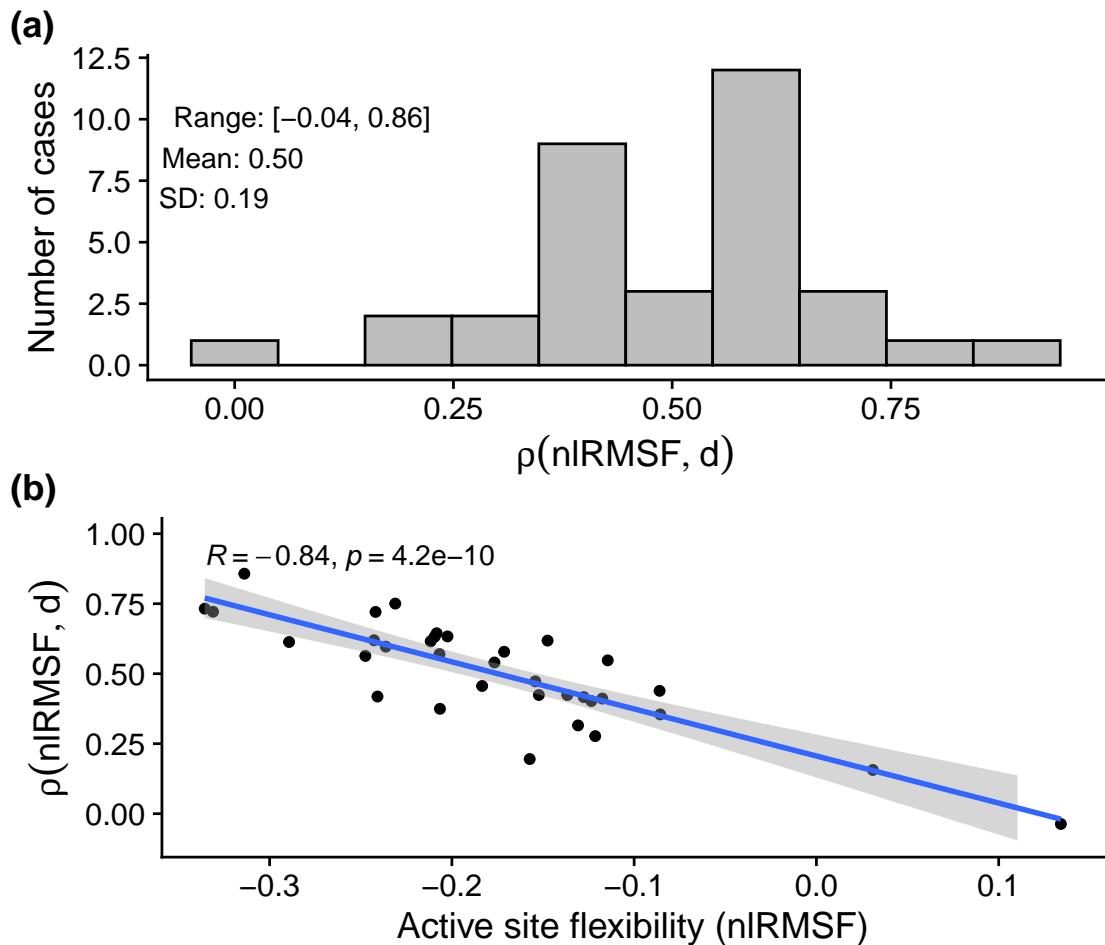


Figure S2: Correlation between flexibility and distance.

3. Model performance

The following table presents the goodness-of-fit metrics for the three models tested: M_1 (flexibility only), M_2 (distance only), and M_{12} (both predictors). For each enzyme family, we report the Akaike Information Criterion (AIC), the deviance explained, the root mean square error between observed and predicted divergence-flexibility trends (RMSE(flex)), the root mean square error between observed and predicted divergence-distance trends (RMSE(dist)), and the relative Shapley contribution of functional constraints to structural divergence (RSC(s_2)). Families are sorted by increasing RSC(s_2).

Table S3: Variation of model performance across all families

M-CSA	PDB	RSC(s_2)	Best	AIC			Expl. Dev.			RMSE(flex)			RMSE(dist)		
				M ₁	M ₂	M ₁₂	M ₁	M ₂	M ₁₂	M ₁	M ₂	M ₁₂	M ₁	M ₂	M ₁₂
749	1nml_A	-0.00	M ₁	714	799	714	0.25	-0.00	0.25	0.06	0.44	0.06	0.28	0.25	0.28
597	1uch_A	0.04	M ₁	346	436	348	0.38	0.03	0.38	0.05	0.39	0.05	0.11	0.10	0.11
858	1mrq_A	0.13	M ₁	645	797	647	0.45	0.11	0.45	0.05	0.41	0.05	0.19	0.08	0.19
258	1sml_A	0.16	M ₁	409	636	412	0.66	0.21	0.66	0.04	0.48	0.05	0.08	0.11	0.09
394	1aj0_A	0.17	M ₁₂	480	660	463	0.57	0.17	0.60	0.03	0.51	0.02	0.15	0.07	0.05
467	1cv2_A	0.20	M ₁	550	634	550	0.36	0.14	0.36	0.04	0.29	0.04	0.14	0.07	0.14
681	1gq8_A	0.21	M ₁	668	782	673	0.45	0.19	0.44	0.05	0.45	0.08	0.21	0.17	0.21
151	1q0n_A	0.24	M ₁₂	224	308	205	0.57	0.25	0.61	0.02	0.42	0.03	0.22	0.10	0.17
109	1d3g_A	0.24	M ₁₂	701	819	688	0.41	0.19	0.44	0.04	0.37	0.04	0.14	0.09	0.09
290	1zio_A	0.26	M ₁₂	293	403	275	0.56	0.27	0.60	0.04	0.34	0.04	0.14	0.03	0.04
257	1xx2_A	0.27	M ₁₂	367	527	358	0.54	0.28	0.56	0.01	0.24	0.01	0.06	0.03	0.03
71	1eug_A	0.27	M ₁₂	153	327	144	0.72	0.39	0.73	0.03	0.27	0.03	0.07	0.03	0.04
98	1bsz_C	0.28	M ₁₂	288	410	287	0.71	0.39	0.71	0.08	0.40	0.07	0.13	0.07	0.09
164	1rvu_A	0.30	M ₁₂	264	297	252	0.40	0.21	0.47	0.08	0.45	0.08	0.23	0.09	0.07
877	1pbg_A	0.31	M ₁₂	784	904	783	0.45	0.27	0.45	0.03	0.24	0.03	0.06	0.03	0.05
328	1lbt_A	0.31	M ₁₂	306	338	298	0.30	0.17	0.35	0.05	0.22	0.06	0.11	0.05	0.05
480	1czf_A	0.33	M ₁₂	566	618	556	0.29	0.18	0.31	0.04	0.24	0.05	0.11	0.06	0.07
216	1ca2_A	0.34	M ₁₂	518	571	505	0.39	0.25	0.43	0.04	0.30	0.04	0.16	0.06	0.07
931	2pth_A	0.35	M ₁₂	366	403	336	0.42	0.27	0.49	0.04	0.37	0.07	0.24	0.08	0.07
15	1znb_A	0.37	M ₁₂	336	396	286	0.51	0.35	0.61	0.08	0.32	0.06	0.21	0.06	0.04
160	1ako_A	0.40	M ₁₂	414	459	389	0.49	0.38	0.54	0.04	0.24	0.04	0.15	0.08	0.08
693	2rnf_A	0.40	M ₁₂	243	261	218	0.39	0.29	0.51	0.08	0.37	0.09	0.31	0.15	0.11
148	1onr_A	0.45	M ₁₂	587	619	575	0.47	0.41	0.50	0.06	0.13	0.04	0.11	0.05	0.06
462	1pnt_A	0.46	M ₁₂	233	252	221	0.56	0.51	0.61	0.06	0.16	0.05	0.13	0.04	0.06
814	1glo_A	0.47	M ₁₂	252	263	212	0.35	0.32	0.47	0.04	0.18	0.03	0.16	0.03	0.02
351	1snz_A	0.49	M ₁₂	697	701	654	0.34	0.33	0.43	0.04	0.25	0.08	0.19	0.04	0.04
2	1btl_A	0.49	M ₁₂	448	455	411	0.36	0.35	0.46	0.04	0.18	0.04	0.20	0.04	0.04
376	1a4l_A	0.50	M ₁₂	781	778	768	0.17	0.17	0.20	0.06	0.13	0.08	0.13	0.06	0.04
923	2acy_A	0.51	M ₁₂	199	197	177	0.41	0.42	0.54	0.09	0.28	0.10	0.29	0.12	0.09
174	9pap_A	0.52	M ₁₂	334	333	315	0.24	0.25	0.31	0.04	0.16	0.06	0.15	0.05	0.05
444	1cel_A	0.57	M ₁₂	820	791	756	0.27	0.32	0.38	0.05	0.15	0.04	0.21	0.04	0.04
252	1igs_A	0.63	M ₁₂	436	377	353	0.37	0.51	0.56	0.04	0.14	0.04	0.26	0.04	0.04
362	1d6o_A	0.68	M ₁₂	189	153	105	0.20	0.43	0.64	0.08	0.32	0.11	0.44	0.11	0.08
908	1rtu_A	0.85	M ₂	249	180	181	0.16	0.56	0.57	0.09	0.08	0.05	0.48	0.07	0.07

RSC(s_2): relative Shapley contribution of functional constraints to structural divergence; Best: model with lowest AIC; Expl. Dev.: deviance explained by each model; RMSE(flex): root mean square error between observed and predicted divergence-flexibility trends; RMSE(dist): RMSE between observed and predicted divergence-distance trends.

4. Robustness analysis

To assess the robustness of our results, we tested whether the model performance metrics are sensitive to methodological choices. Specifically, we examined robustness with respect to: (1) reference protein choice, comparing results when using the reference protein (ca_ref) versus the structurally closest homolog (ca_hom, selected based on lowest overall RMSD to reduce artifacts from gaps and non-evolutionary structural differences); and (2) atom choice, comparing results when using C α atoms (ca_ref) versus C β atoms (cb_ref) for structural calculations.

Results show that the choice of reference protein has minimal impact: goodness-of-fit metrics exhibit strong correlations between the two approaches, and average values are nearly identical, confirming robustness to this methodological choice. In contrast, while C α - and C β -based analyses show significant correlations, the correlations are weaker and C β -based analyses consistently yield lower goodness-of-fit values across all metrics, supporting our choice to use C α atoms for the main analyses.

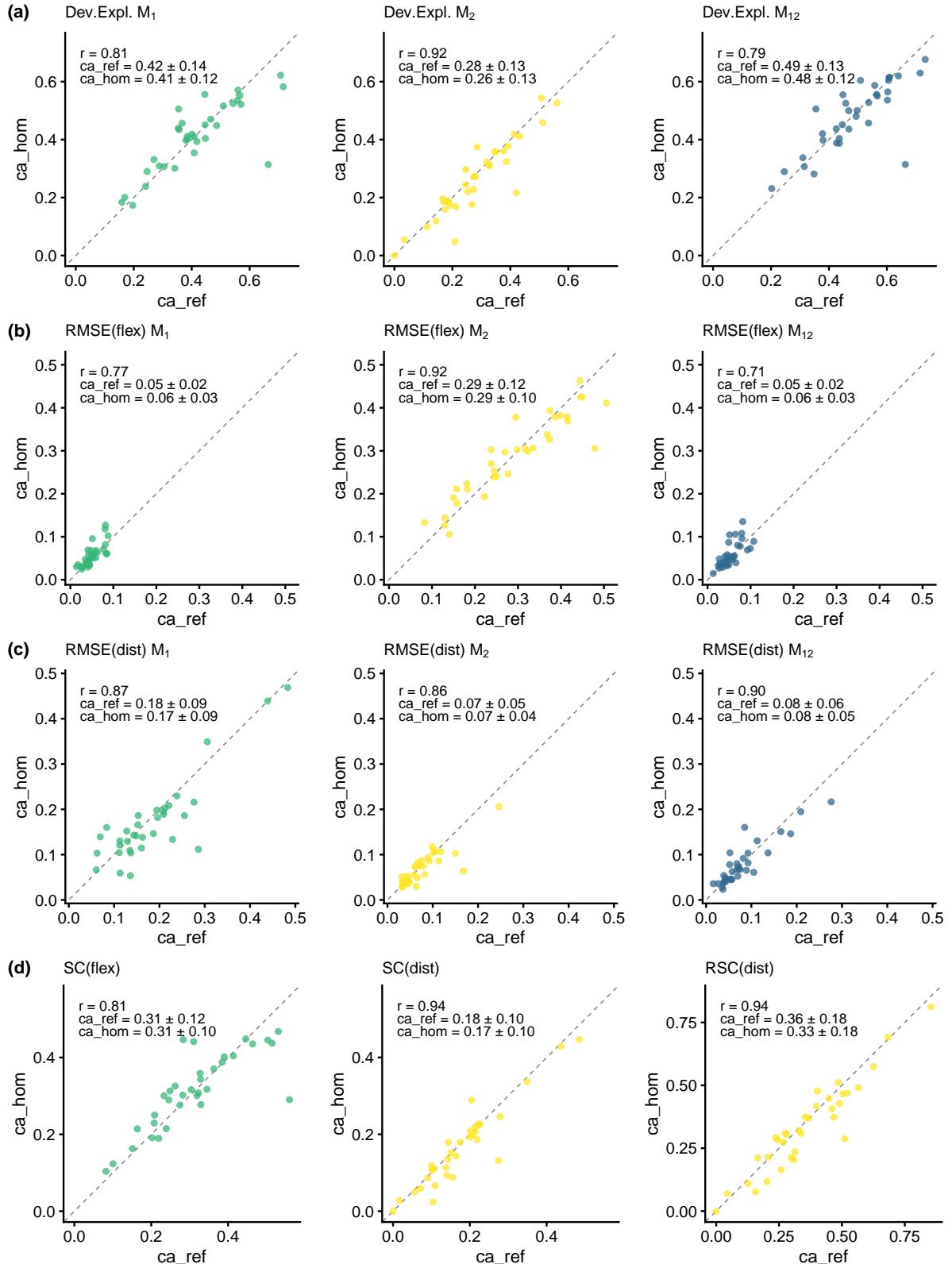


Figure S3: Robustness to reference protein choice. Each panel compares goodness-of-fit metrics between analyses using the reference protein (ca_{ref}) and a homolog (ca_{hom}). (a) Deviance explained for models M₁, M₂, and M₁₂. (b) RMSE between observed and predicted divergence-flexibility trends. (c) RMSE between observed and predicted divergence-distance trends. (d) Shapley contributions: SC(flex), SC(dist), and RSC(dist).

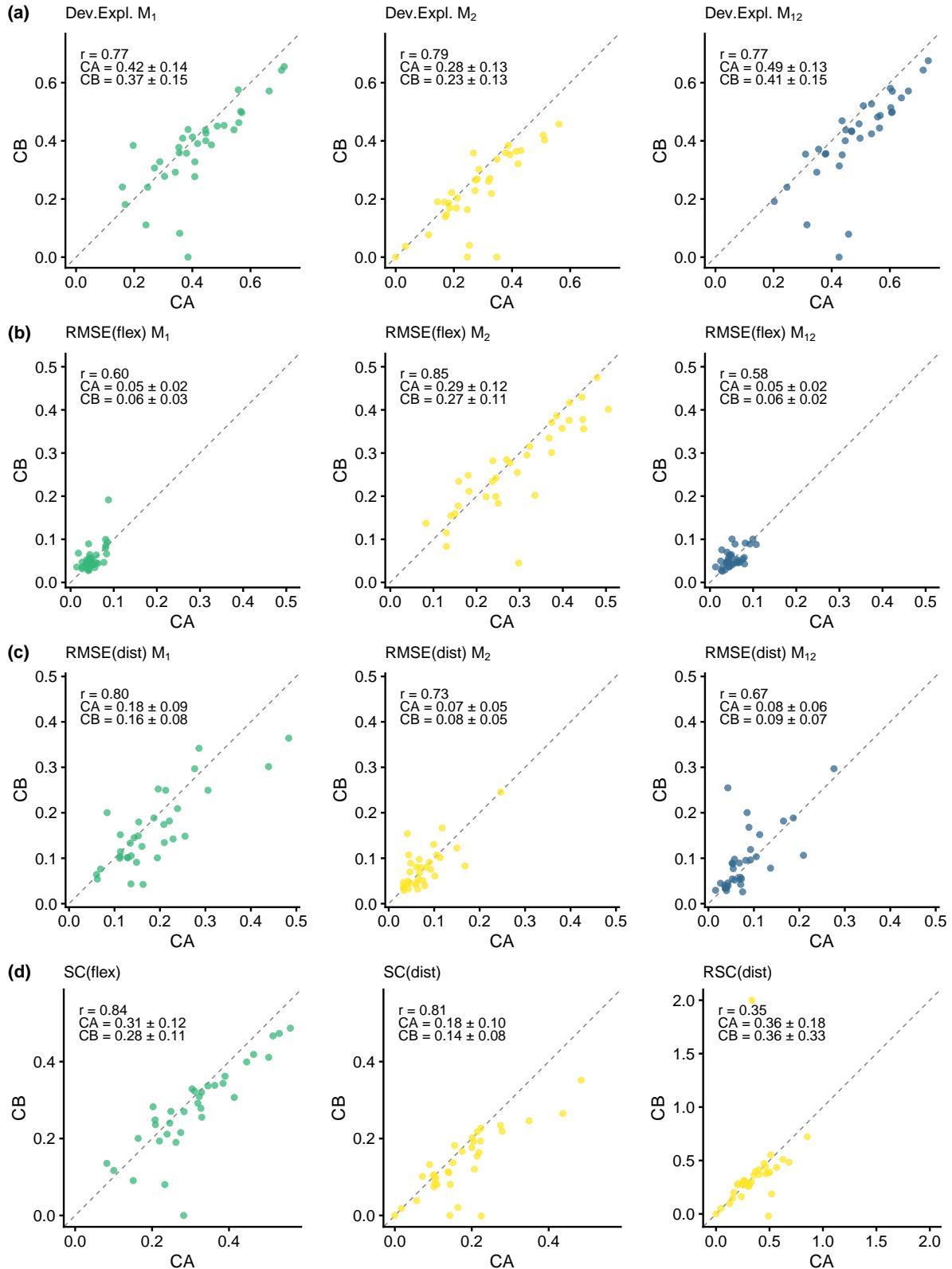


Figure S4: Robustness to atom choice. Each panel compares goodness-of-fit metrics between analyses using C α atoms (CA) and C β atoms (CB). (a) Deviance explained for models M₁, M₂, and M₁₂. (b) RMSE between observed and predicted divergence-flexibility trends. (c) RMSE between observed and predicted divergence-distance trends. (d) Shapley contributions: SC(flex), SC(dist), and RSC(dist).

5. Active site conservation

We analyze structural divergence at active site residues ($d = 0$). For each family, divergence metrics are family-normalized, and M_{12} predictions are decomposed into per-residue s_1 (non-functional constraint) and s_2 (functional constraint) contributions. For each active site residue, we calculate the relative magnitude $rs_1 = |s_1|/(|s_1| + |s_2|)$ and $rs_2 = |s_2|/(|s_1| + |s_2|)$. The values reported in the tables below (s_1 , s_2 , rs_1 , rs_2) are the means of these per-residue metrics over all active site residues within each family.

Table S4: Summary statistics for active site divergence

Statistic	Obs	M_{12}	s_1	s_2	rs_1	rs_2
Mean	-0.62	-0.69	-0.32	-0.38	0.52	0.48
SD	0.28	0.22	0.20	0.28	0.29	0.29
Min	-1.07	-1.06	-0.78	-1.03	0.03	0.00
Max	0.25	-0.26	0.15	-0.00	1.00	0.97

Obs: observed nRMSD; M_{12} : predicted nRMSD; s_1 : non-functional constraint contribution; s_2 : functional constraint contribution; rs_1 , rs_2 : relative magnitude contributions. Statistics calculated across 33 enzyme families (case 749 excluded). All values are family-averaged active site metrics ($d = 0$).

Table S5: Active site structural divergence and constraint contributions

M-CSA	Whole-protein			Active site							
	SC(s_1)	SC(s_2)	RSC(s_2)	nIRMSF	Obs	M_{12}	s_1	s_2	rs_1	rs_2	
597	0.36	0.02	0.04	-0.21	-0.40 -0.38	-0.38 -0.00	1.00	0.00			
858	0.39	0.06	0.13	-0.21	-0.68 -0.57	-0.57 -0.00	1.00	0.00			
258	0.56	0.10	0.16	-0.16	-0.37 -0.26	-0.26 -0.00	1.00	0.00			
394	0.50	0.10	0.17	-0.12	-0.89 -0.88	-0.32 -0.56	0.32	0.68			
467	0.28	0.07	0.20	-0.20	-0.54 -0.53	-0.53 -0.00	1.00	0.00			
681	0.35	0.09	0.21	-0.24	-0.76 -0.75	-0.75 -0.00	1.00	0.00			
151	0.46	0.14	0.24	-0.18	-0.04 -0.39	-0.29 -0.09	0.72	0.28			
109	0.33	0.11	0.24	-0.09	0.25 -0.29	-0.16 -0.13	0.63	0.37			
290	0.45	0.16	0.26	-0.18	-0.42 -0.38	-0.22 -0.15	0.69	0.31			
257	0.41	0.15	0.27	-0.21	-0.60 -0.64	-0.36 -0.28	0.54	0.46			
71	0.53	0.20	0.27	-0.25	-0.47 -0.49	-0.42 -0.07	0.85	0.15			
98	0.51	0.20	0.28	-0.34	-0.93 -0.96	-0.78 -0.18	0.81	0.19			
164	0.33	0.14	0.30	-0.13	-0.42 -0.67	-0.20 -0.47	0.35	0.65			
877	0.31	0.14	0.31	-0.23	-0.81 -0.73	-0.51 -0.22	0.70	0.30			
328	0.24	0.11	0.31	-0.15	-0.61 -0.73	-0.25 -0.48	0.34	0.66			
480	0.21	0.10	0.33	-0.21	-0.67 -0.61	-0.36 -0.25	0.58	0.42			
216	0.28	0.14	0.34	-0.11	-0.90 -0.91	-0.27 -0.64	0.40	0.60			
931	0.32	0.17	0.35	-0.15	-0.80 -0.83	-0.23 -0.60	0.27	0.73			
15	0.38	0.22	0.37	-0.15	-0.83 -0.81	-0.20 -0.60	0.35	0.65			
160	0.32	0.21	0.40	-0.29	-1.07 -1.02	-0.51 -0.51	0.46	0.54			
693	0.30	0.20	0.40	-0.09	-0.84 -1.01	-0.15 -0.87	0.22	0.78			
148	0.27	0.22	0.45	-0.31	-0.55 -0.67	-0.56 -0.11	0.83	0.17			
462	0.33	0.28	0.46	-0.33	-0.93 -0.93	-0.55 -0.38	0.55	0.45			
814	0.25	0.22	0.47	-0.12	-0.54 -0.62	-0.13 -0.49	0.21	0.79			
351	0.22	0.21	0.49	-0.24	-0.69 -0.79	-0.32 -0.47	0.40	0.60			
2	0.23	0.22	0.49	-0.21	-0.80 -0.89	-0.30 -0.59	0.32	0.68			
376	0.10	0.10	0.50	-0.24	-0.98 -0.96	-0.20 -0.77	0.20	0.80			
923	0.26	0.27	0.51	-0.12	-0.24 -0.45	-0.18 -0.27	0.39	0.61			
174	0.15	0.16	0.52	-0.14	-0.27 -0.48	-0.12 -0.36	0.23	0.77			
444	0.16	0.21	0.57	-0.24	-0.69 -0.64	-0.29 -0.35	0.44	0.56			
252	0.21	0.35	0.63	-0.17	-0.76 -0.81	-0.17 -0.65	0.20	0.80			
362	0.20	0.44	0.68	0.13	-0.50 -0.68	0.15 -0.83	0.20	0.80			
908	0.08	0.48	0.85	-0.13	-0.76 -1.06	-0.03 -1.03	0.03	0.97			

Values represent family-averaged metrics for active site residues ($d = 0$). Obs: observed nIRMSD; M_{12} : predicted nIRMSD; s_1 : non-functional constraint contribution; s_2 : functional constraint contribution; rs_1 , rs_2 : relative magnitude contributions; SC(s_1), SC(s_2): Shapley constraint contributions (whole-family level); RSC(s_2): relative Shapley contribution of s_2 ; nIRMSF: mean normalized flexibility at active site. Case 749 excluded as outlier. Families sorted by RSC(s_2).

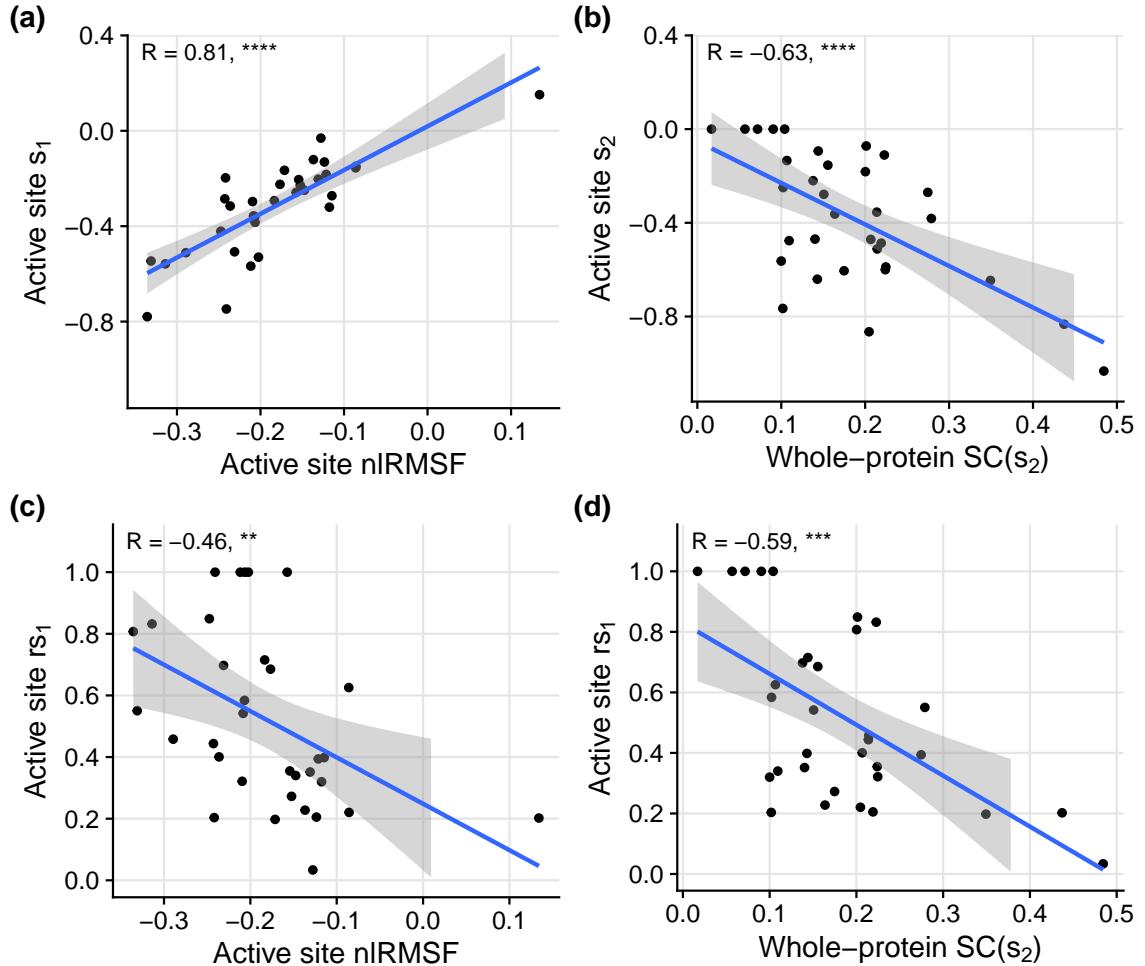


Figure S5: Active site constraint correlations. (a) Relationship between active site non-functional constraint contribution (s_1) and active site flexibility (nIRMSF). (b) Relationship between active site functional constraint contribution (s_2) and whole-protein Shapley contribution $SC(s_2)$. (c) Relationship between active site relative non-functional contribution (rs_1) and active site flexibility. (d) Relationship between active site relative non-functional contribution (rs_1) and whole-protein Shapley contribution $SC(s_2)$. All metrics are family-averaged over active site residues ($d = 0$). Lines show linear regression fits with 95% confidence intervals. Correlation statistics displayed on each panel.

6. Family by family analysis

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.

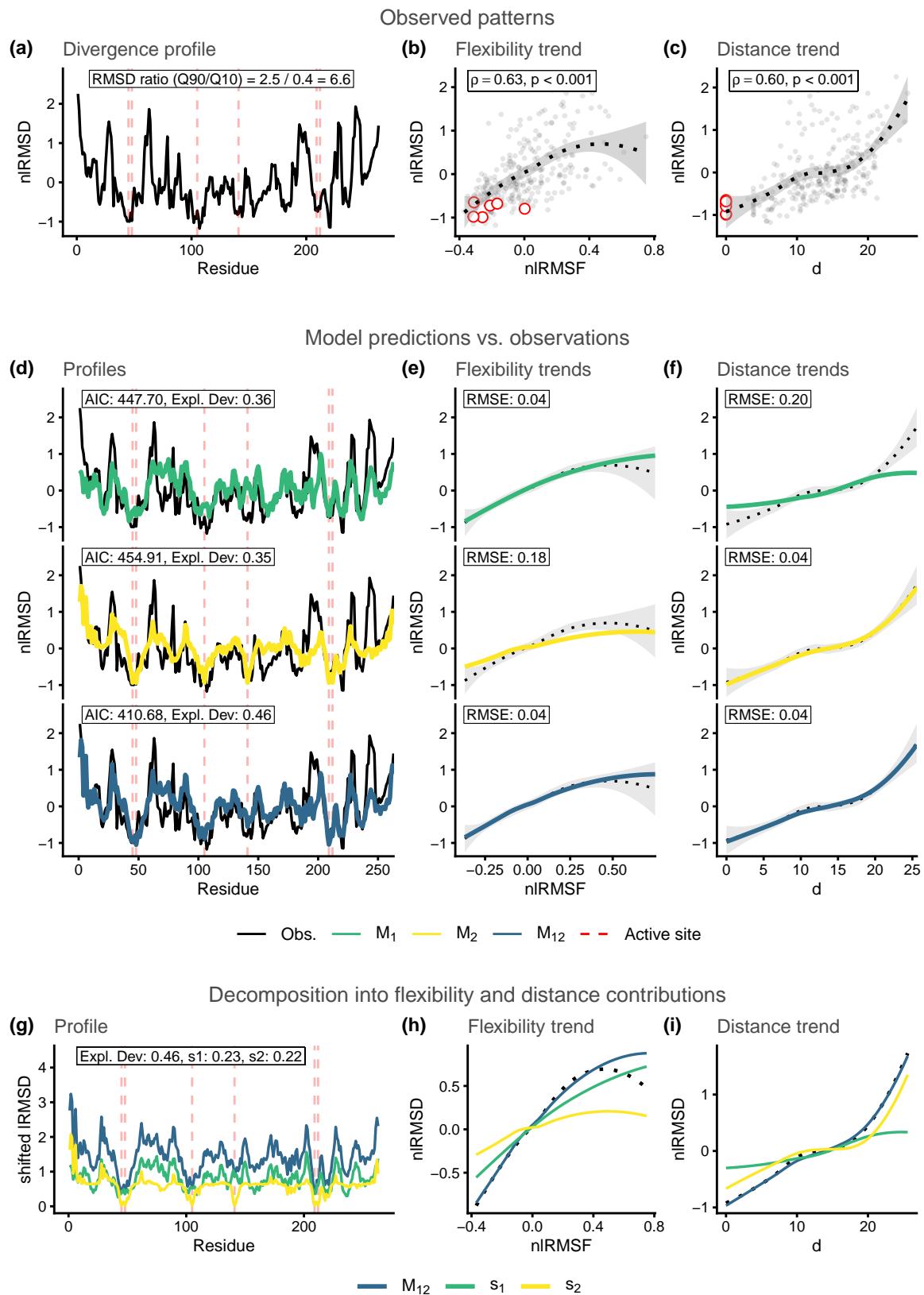


Figure S6: Structural divergence analysis for enzyme family MCSA ID: 2. Reference protein PDB ID: 1btl_A.

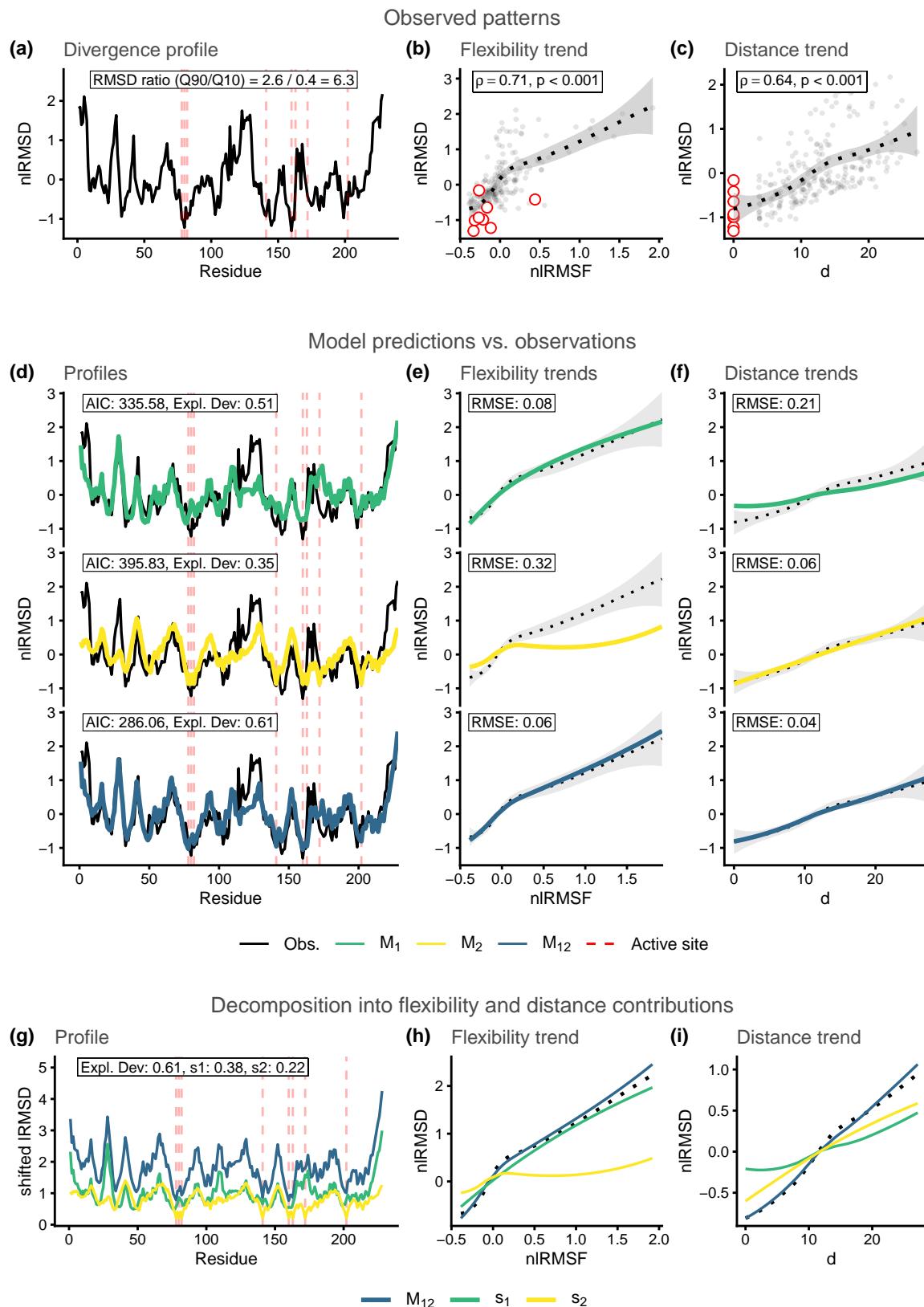


Figure S7: Structural divergence analysis for enzyme family MCSA ID: 15. Reference protein PDB ID: 1znb_A.

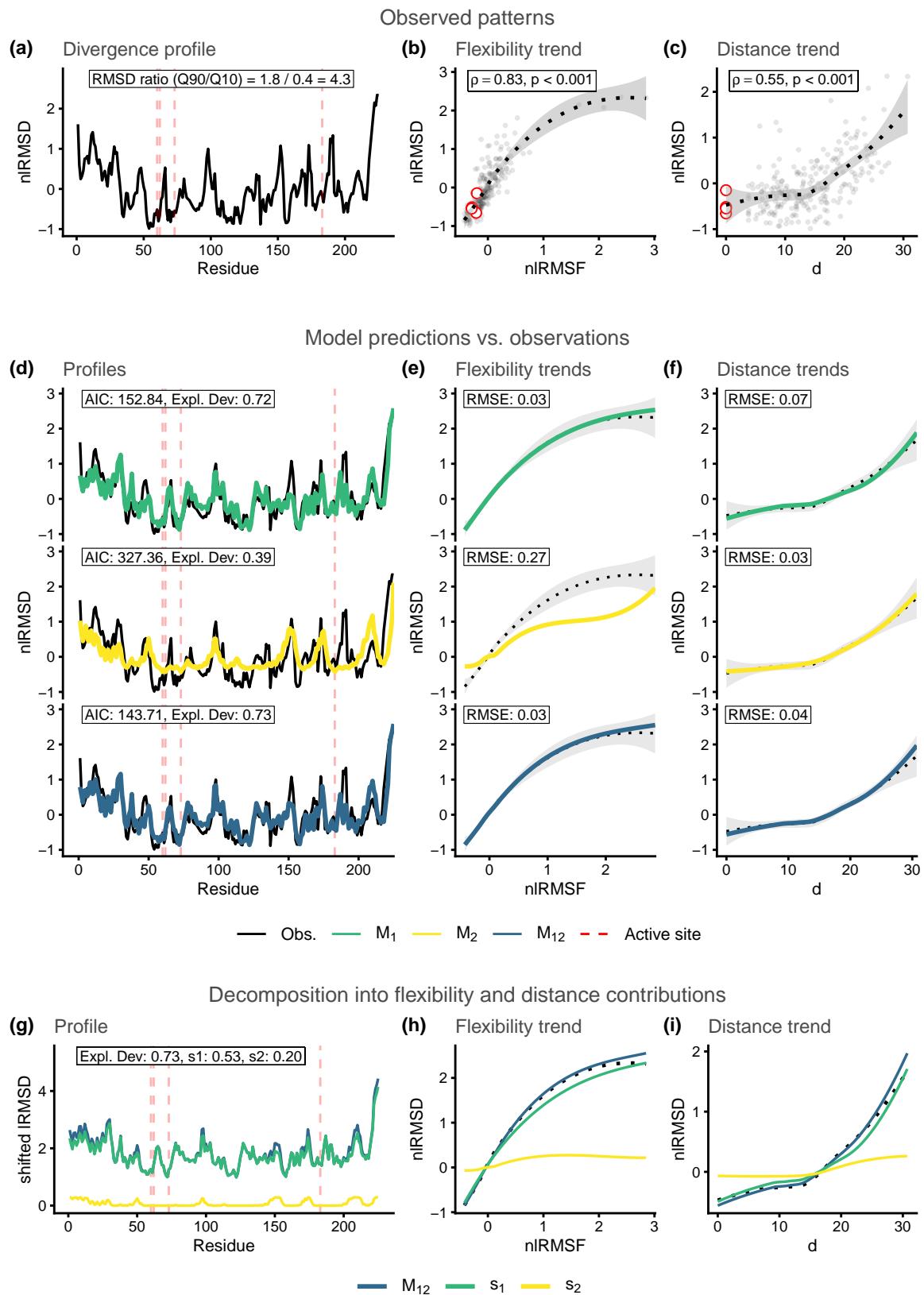


Figure S8: Structural divergence analysis for enzyme family MCSA ID: 71. Reference protein PDB ID: 1eug_A.

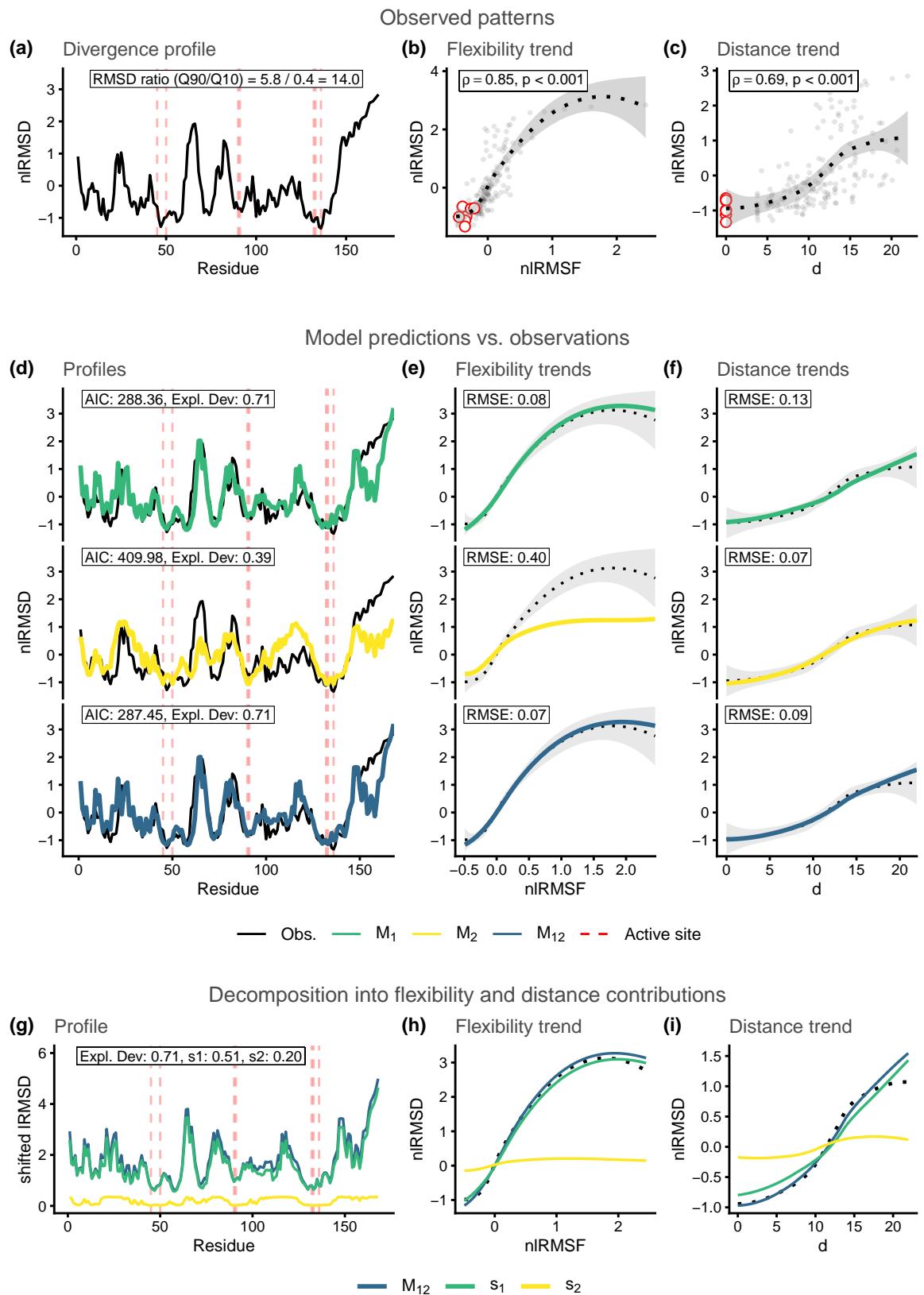


Figure S9: Structural divergence analysis for enzyme family MCSA ID: 98. Reference protein PDB ID: 1bsz_C.

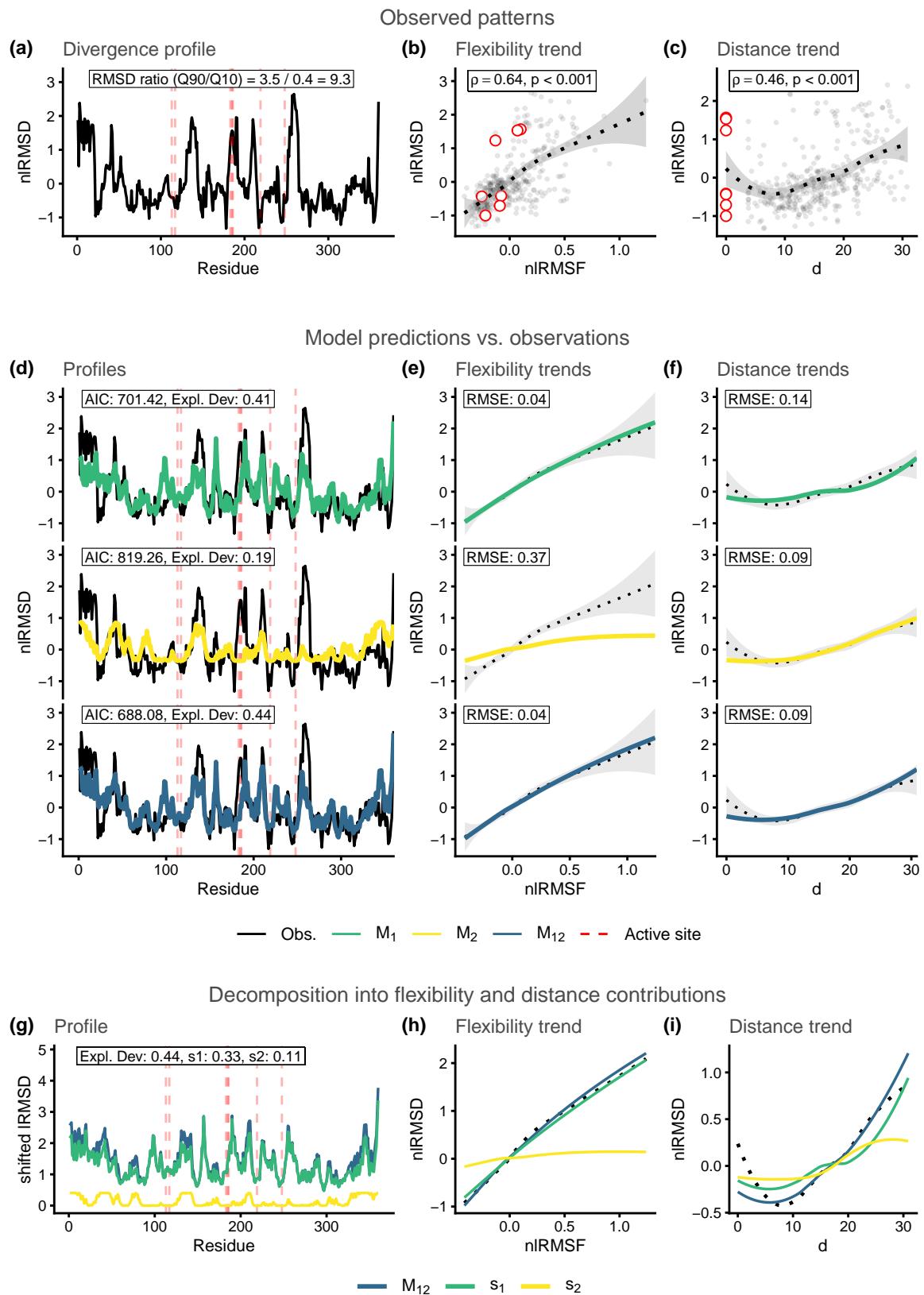


Figure S10: Structural divergence analysis for enzyme family MCSA ID: 109. Reference protein PDB ID: 1d3g_A.

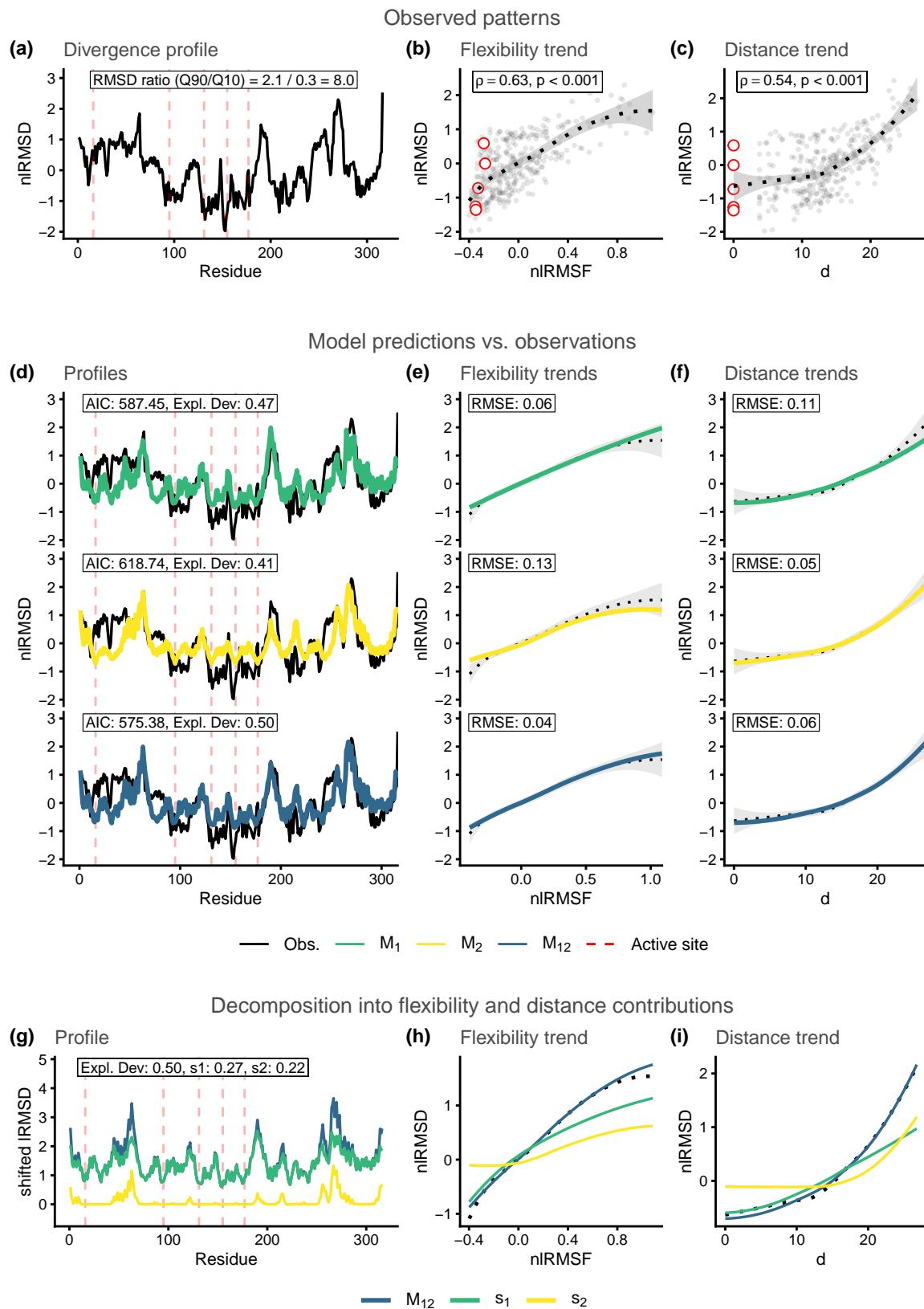


Figure S11: Structural divergence analysis for enzyme family MCSA ID: 148. Reference protein PDB ID: 1onr_A.

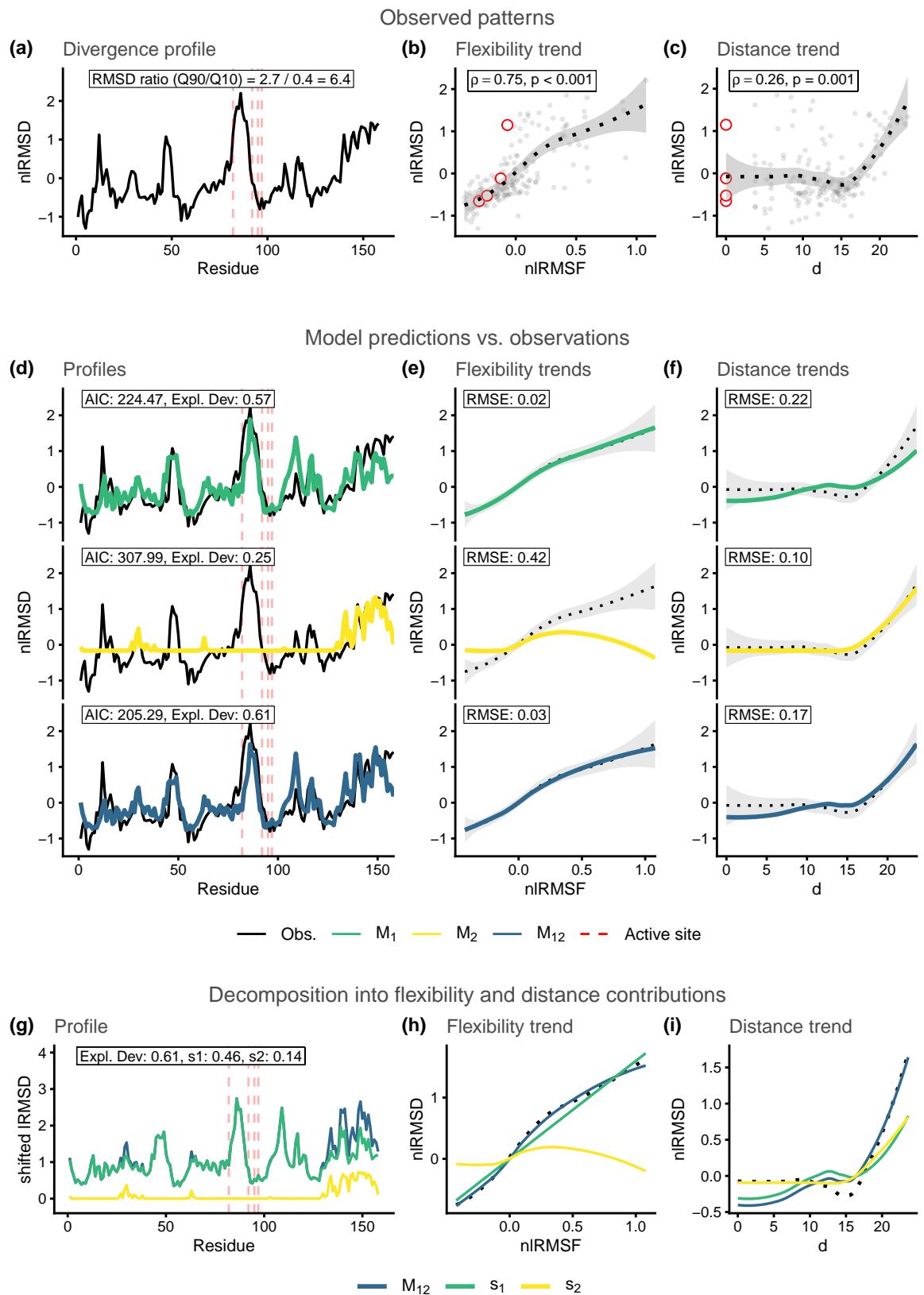


Figure S12: Structural divergence analysis for enzyme family MCSA ID: 151. Reference protein PDB ID: 1q0n_A.

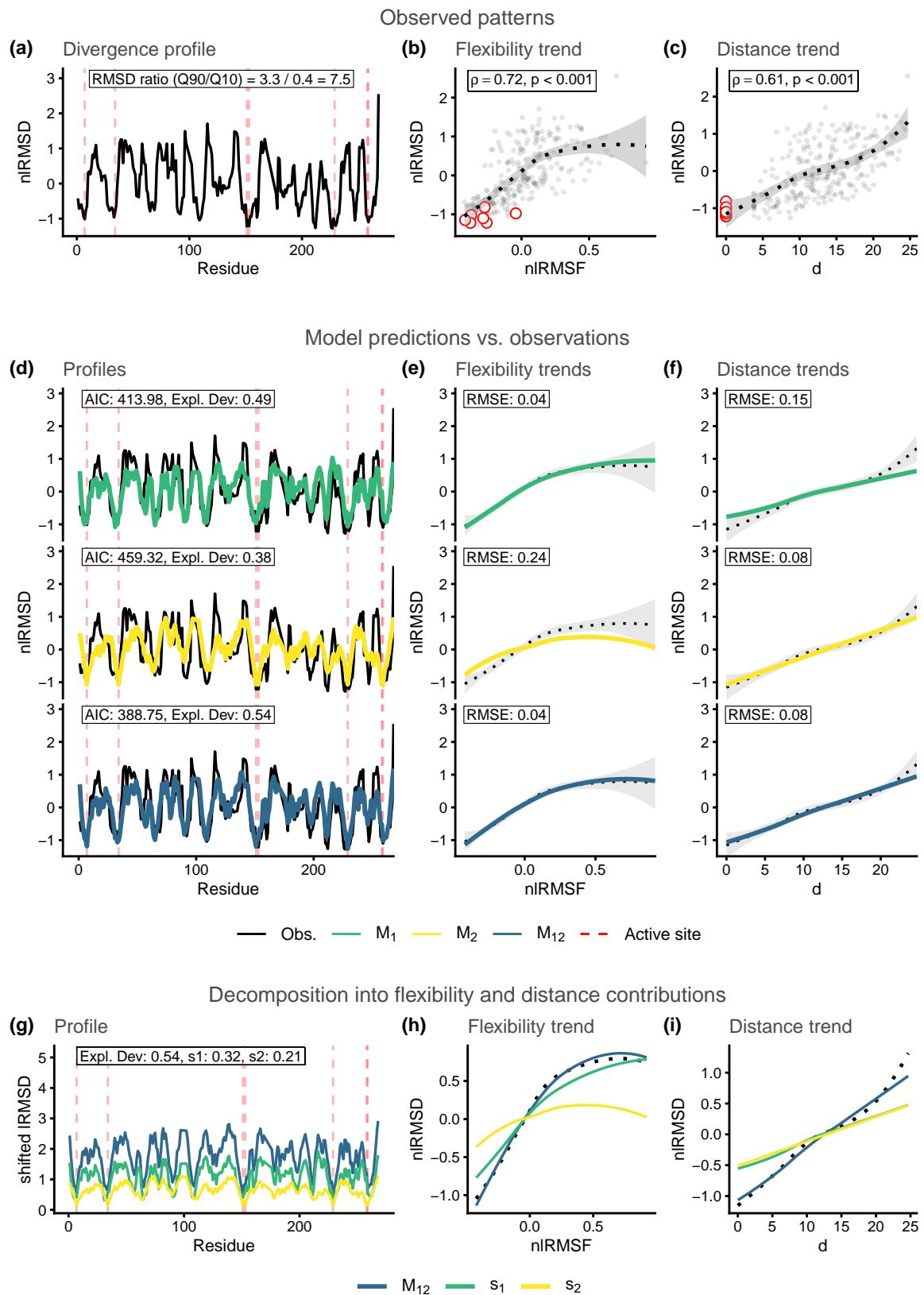


Figure S13: Structural divergence analysis for enzyme family MCSA ID: 160. Reference protein PDB ID: 1ako_A.

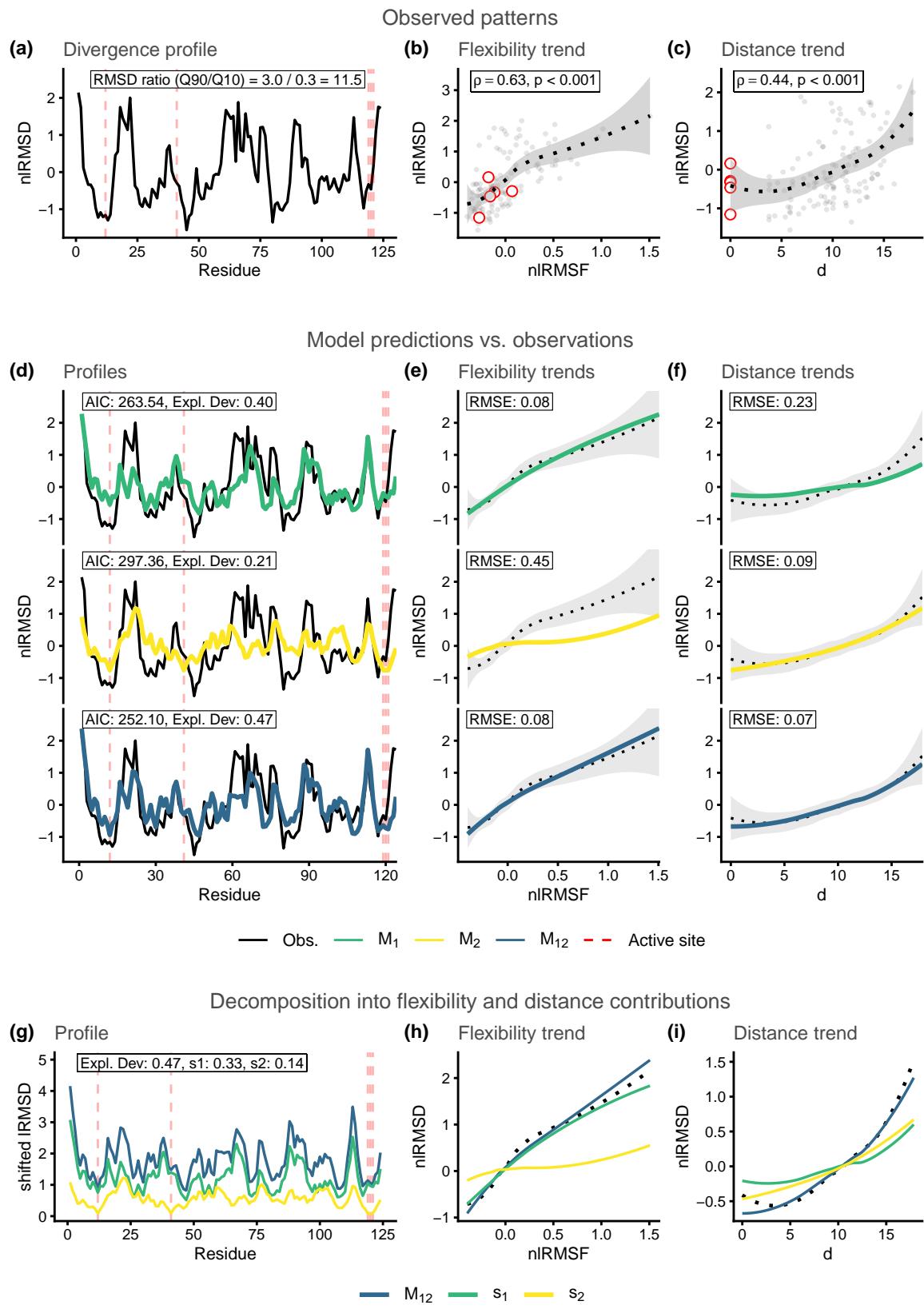


Figure S14: Structural divergence analysis for enzyme family MCSA ID: 164. Reference protein PDB ID: 1ruv_A.

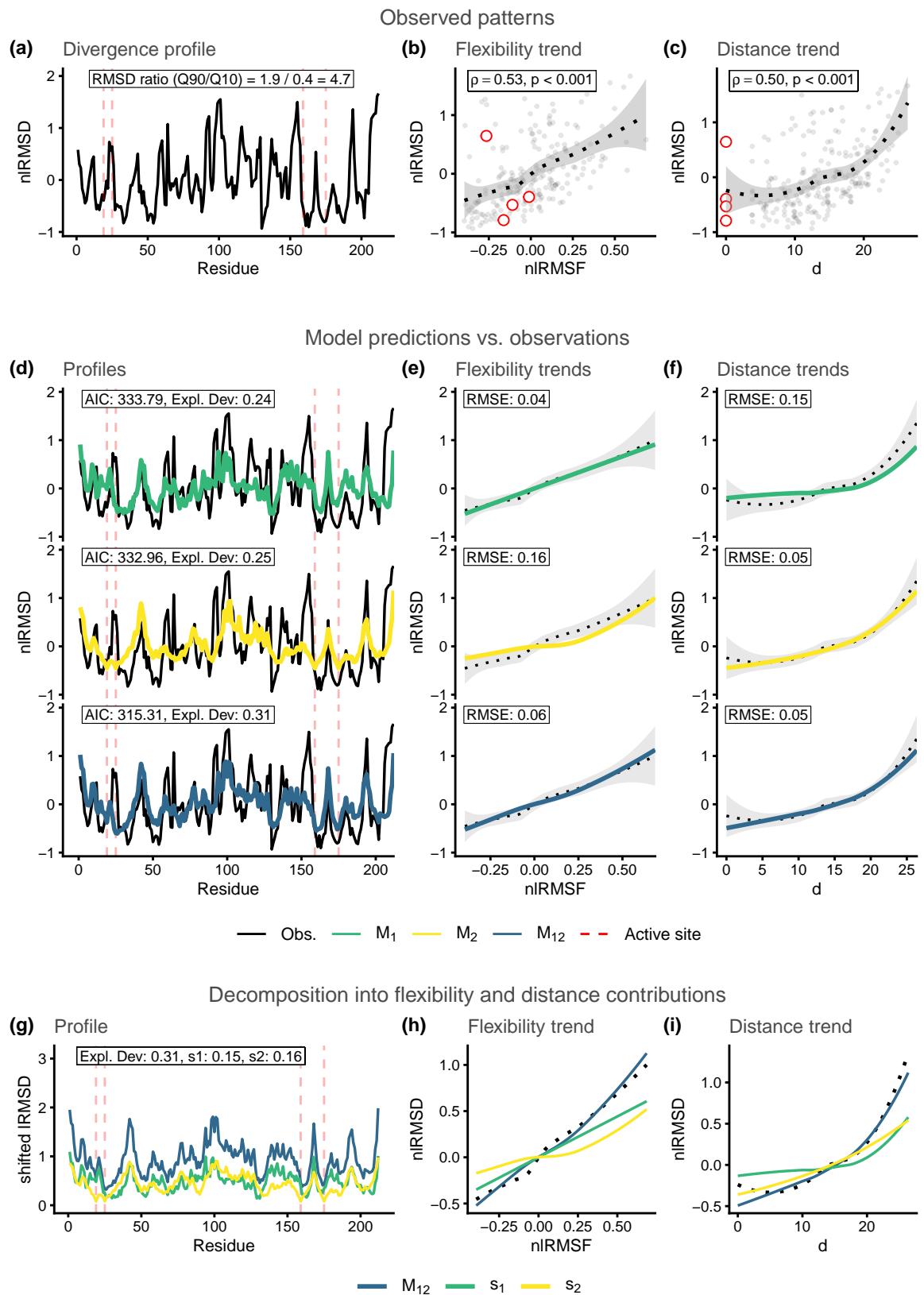


Figure S15: Structural divergence analysis for enzyme family MCSA ID: 174. Reference protein PDB ID: 9pap_A.

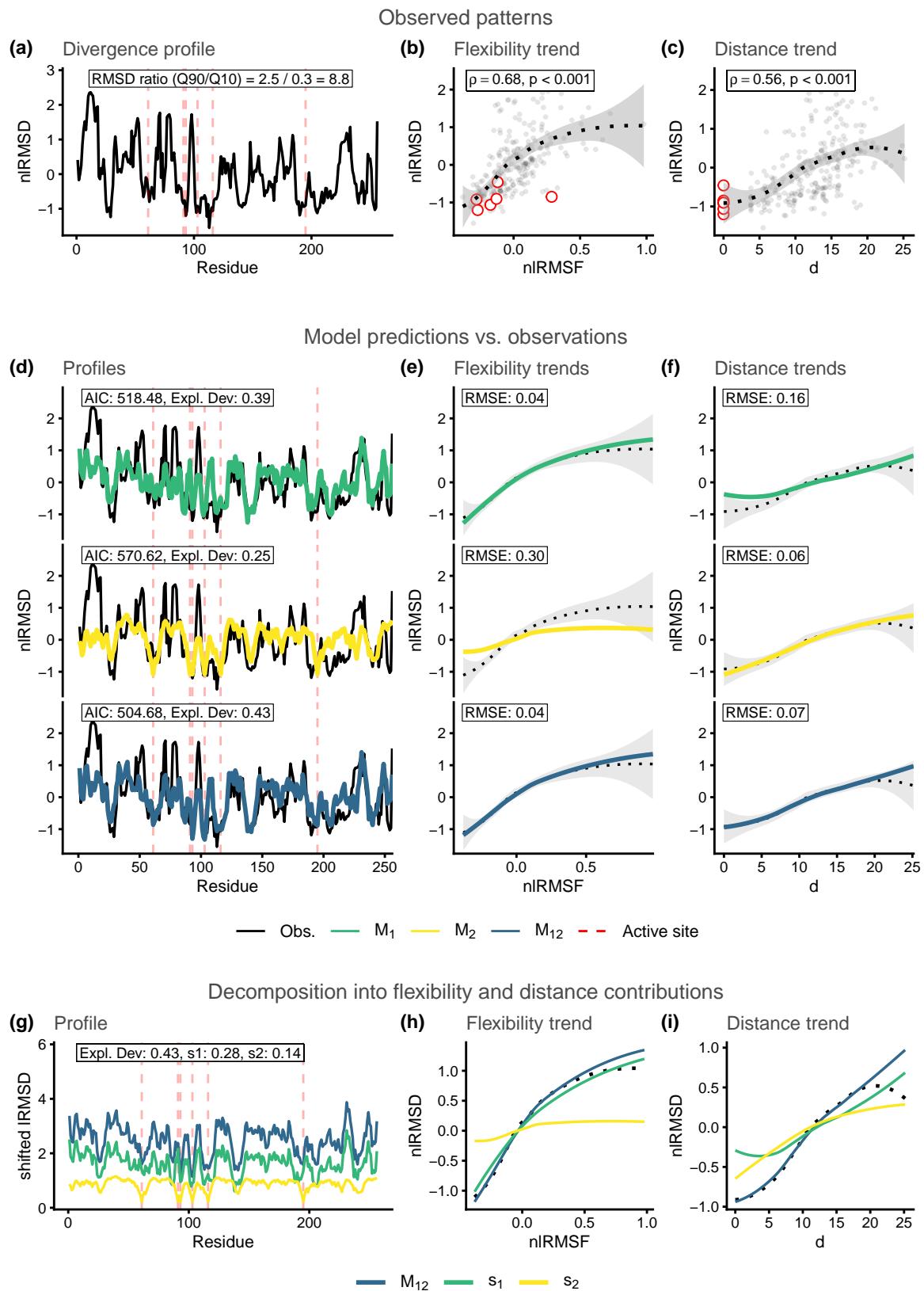


Figure S16: Structural divergence analysis for enzyme family MCSA ID: 216. Reference protein PDB ID: 1ca2_A.

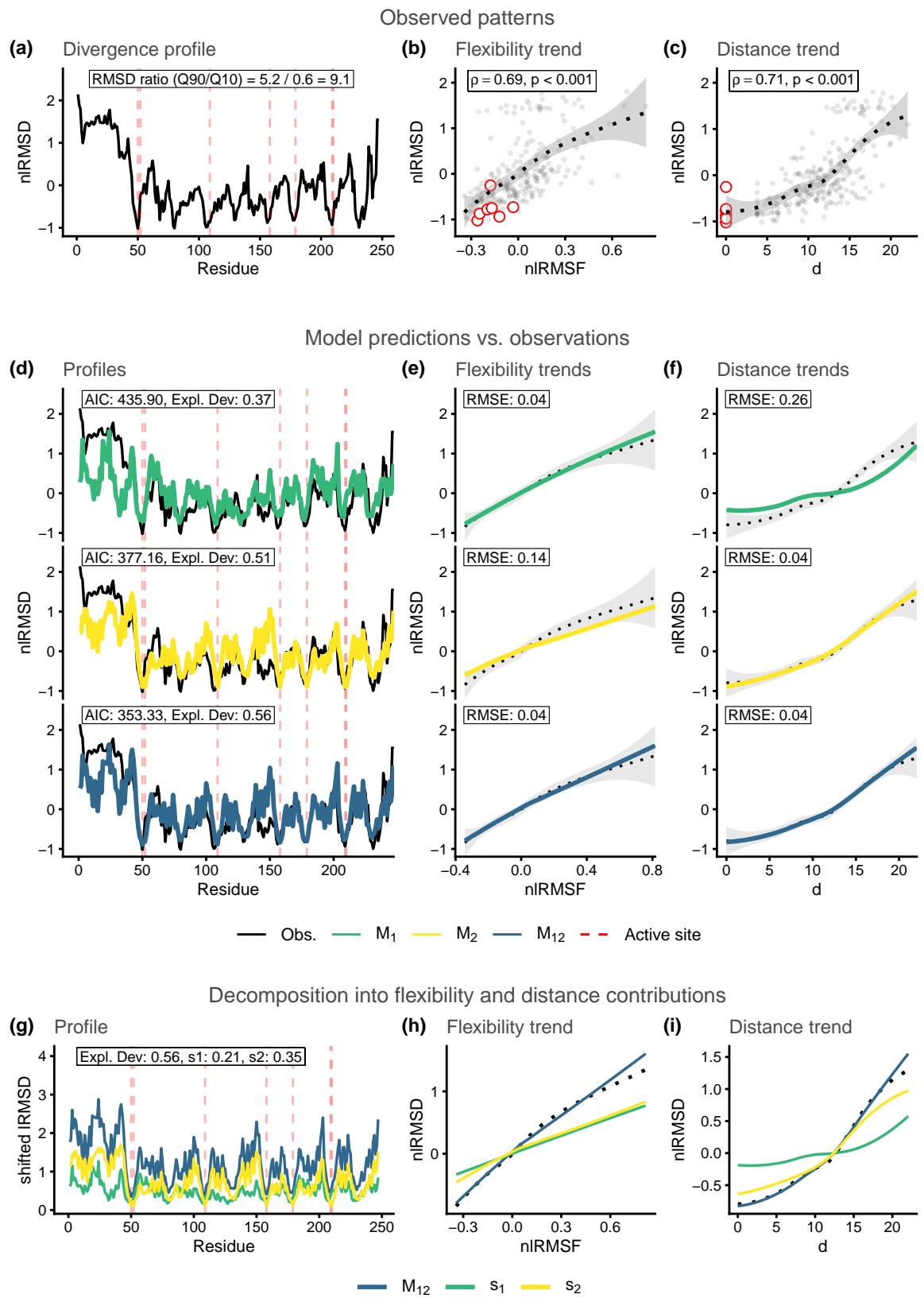


Figure S17: Structural divergence analysis for enzyme family MCSA ID: 252. Reference protein PDB ID: 1igs_A.

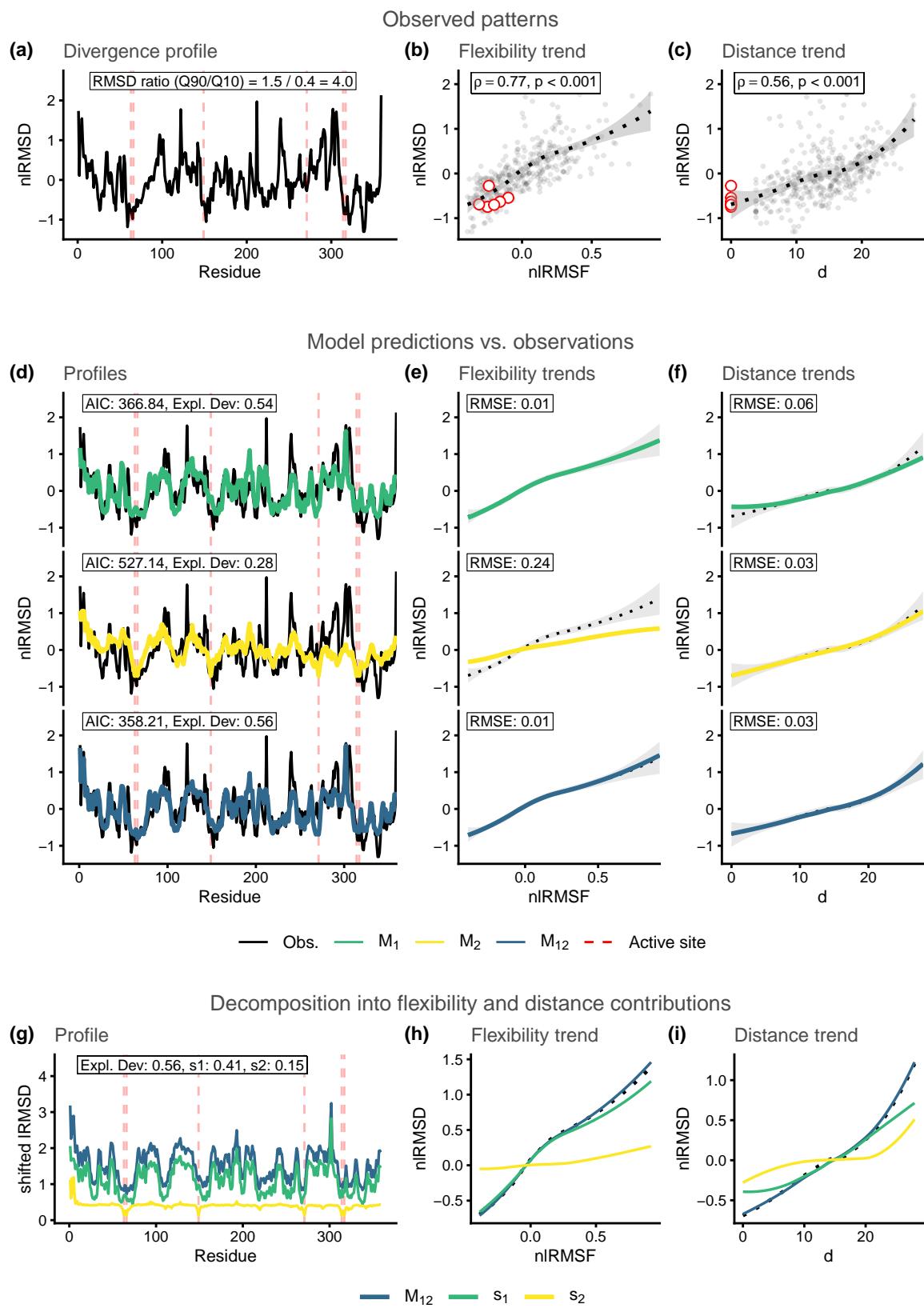


Figure S18: Structural divergence analysis for enzyme family MCSA ID: 257. Reference protein PDB ID: 1xx2_A.

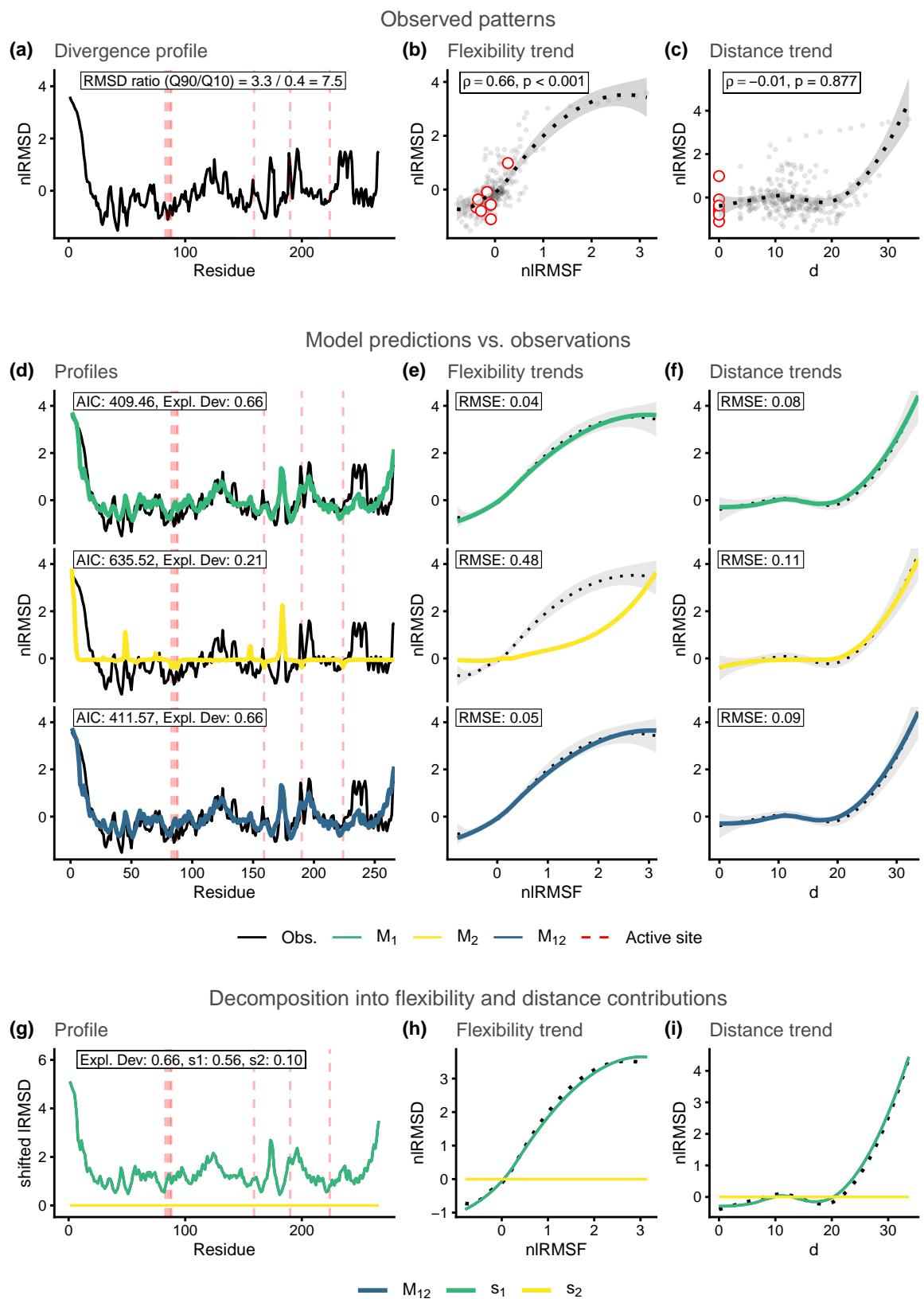


Figure S19: Structural divergence analysis for enzyme family MCSA ID: 258. Reference protein PDB ID: 1sml_A.

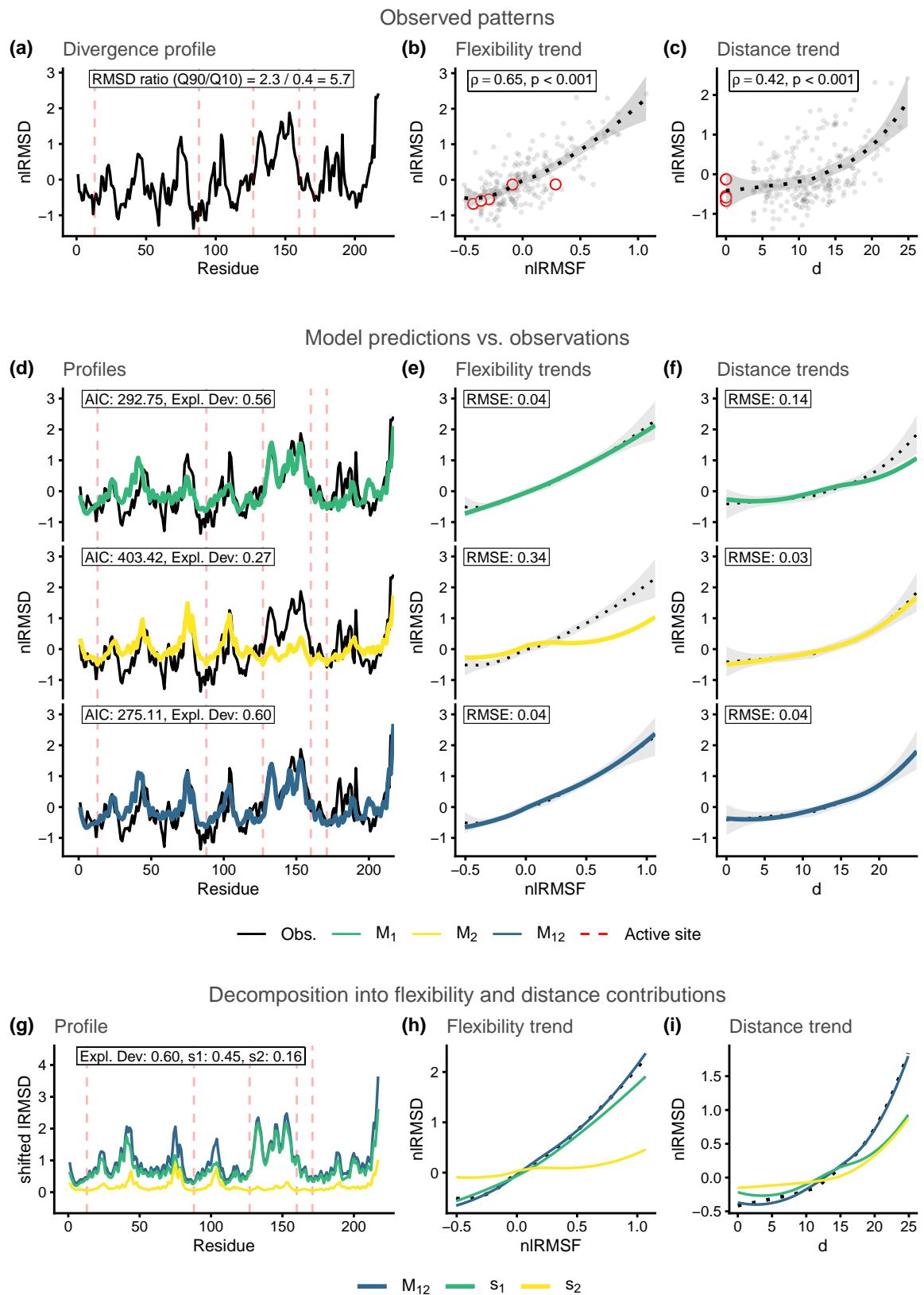


Figure S20: Structural divergence analysis for enzyme family MCSA ID: 290. Reference protein PDB ID: 1zio_A.

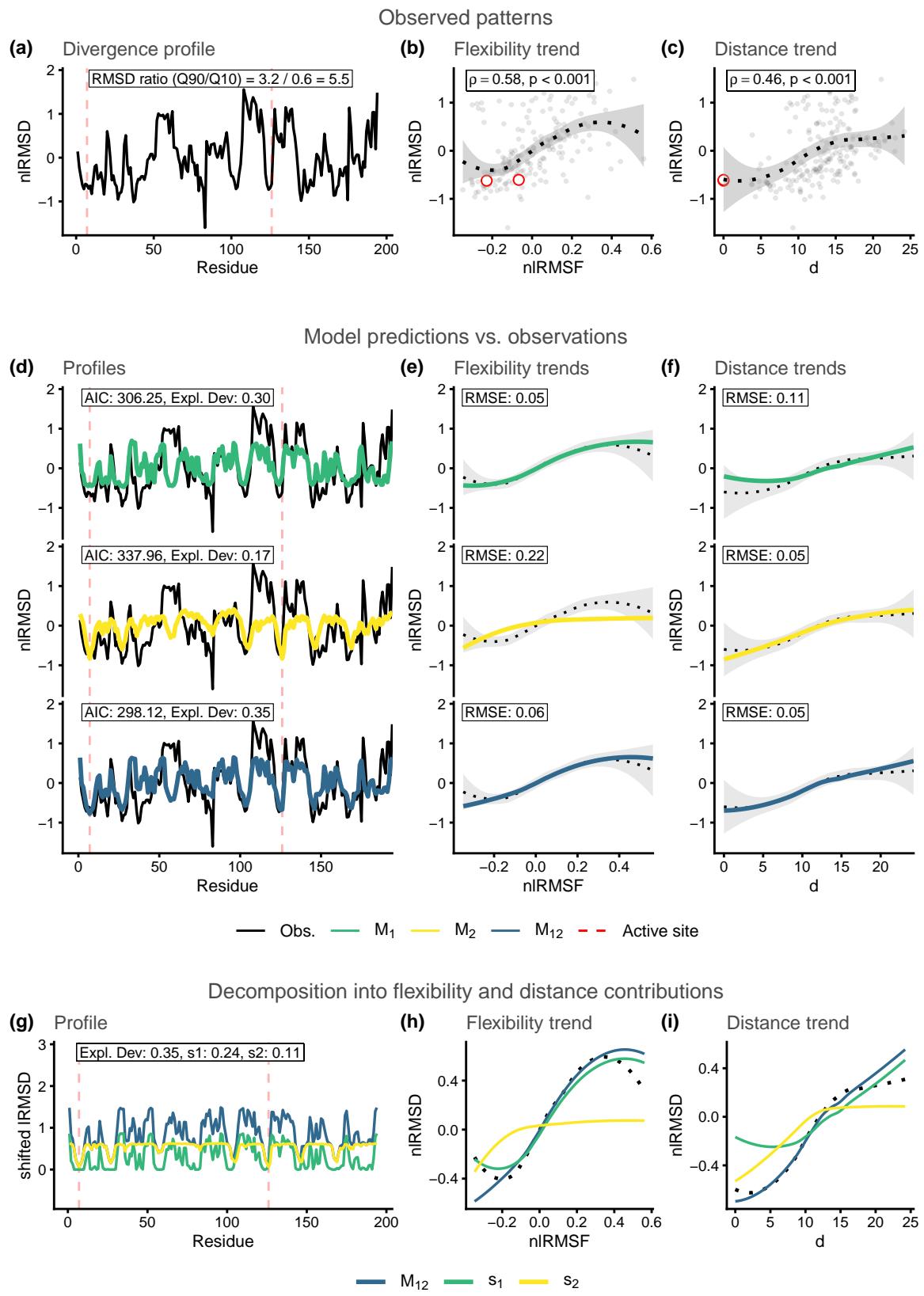


Figure S21: Structural divergence analysis for enzyme family MCSA ID: 328. Reference protein PDB ID: 1lbt_A.

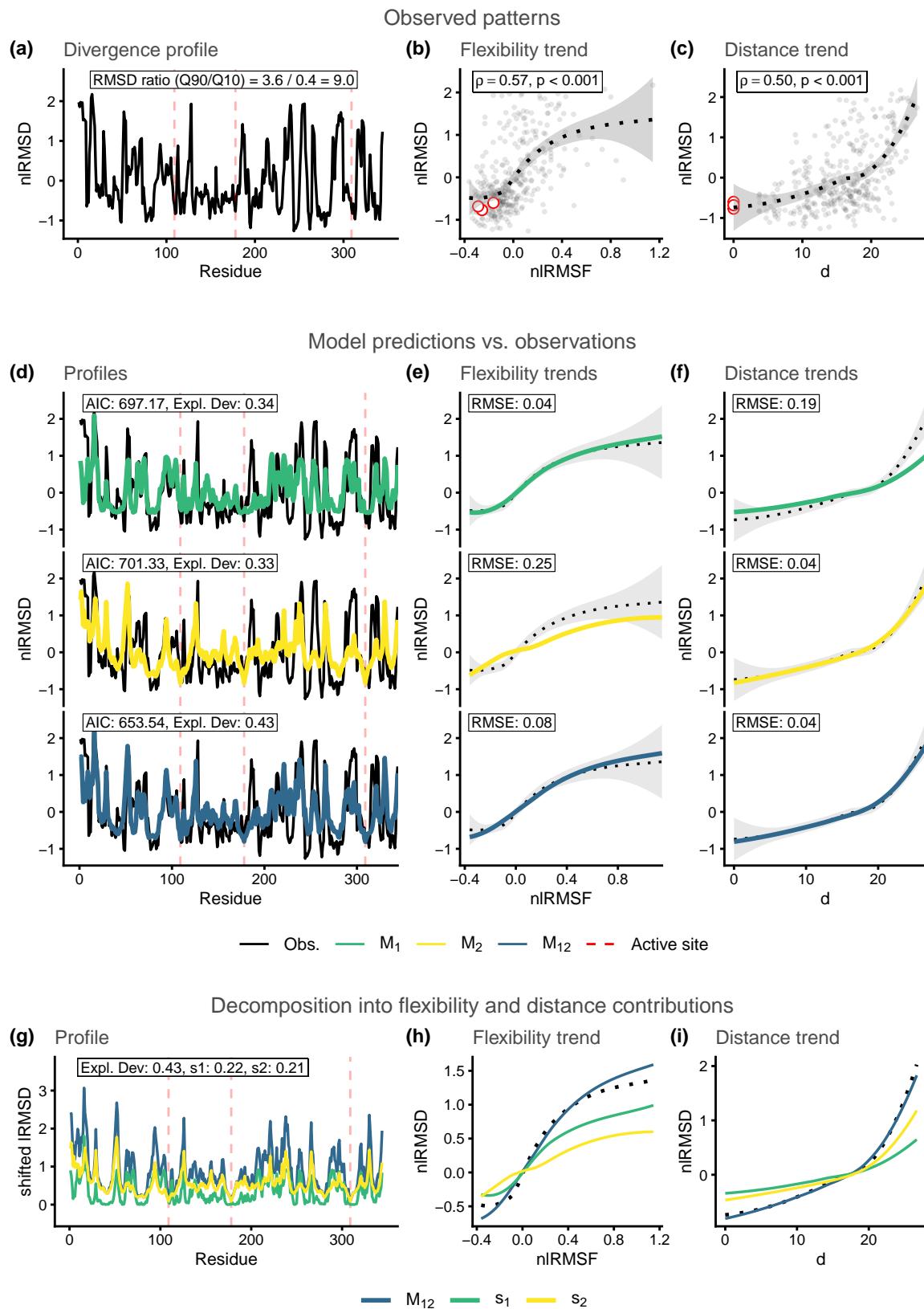


Figure S22: Structural divergence analysis for enzyme family MCSA ID: 351. Reference protein PDB ID: 1snz_A.

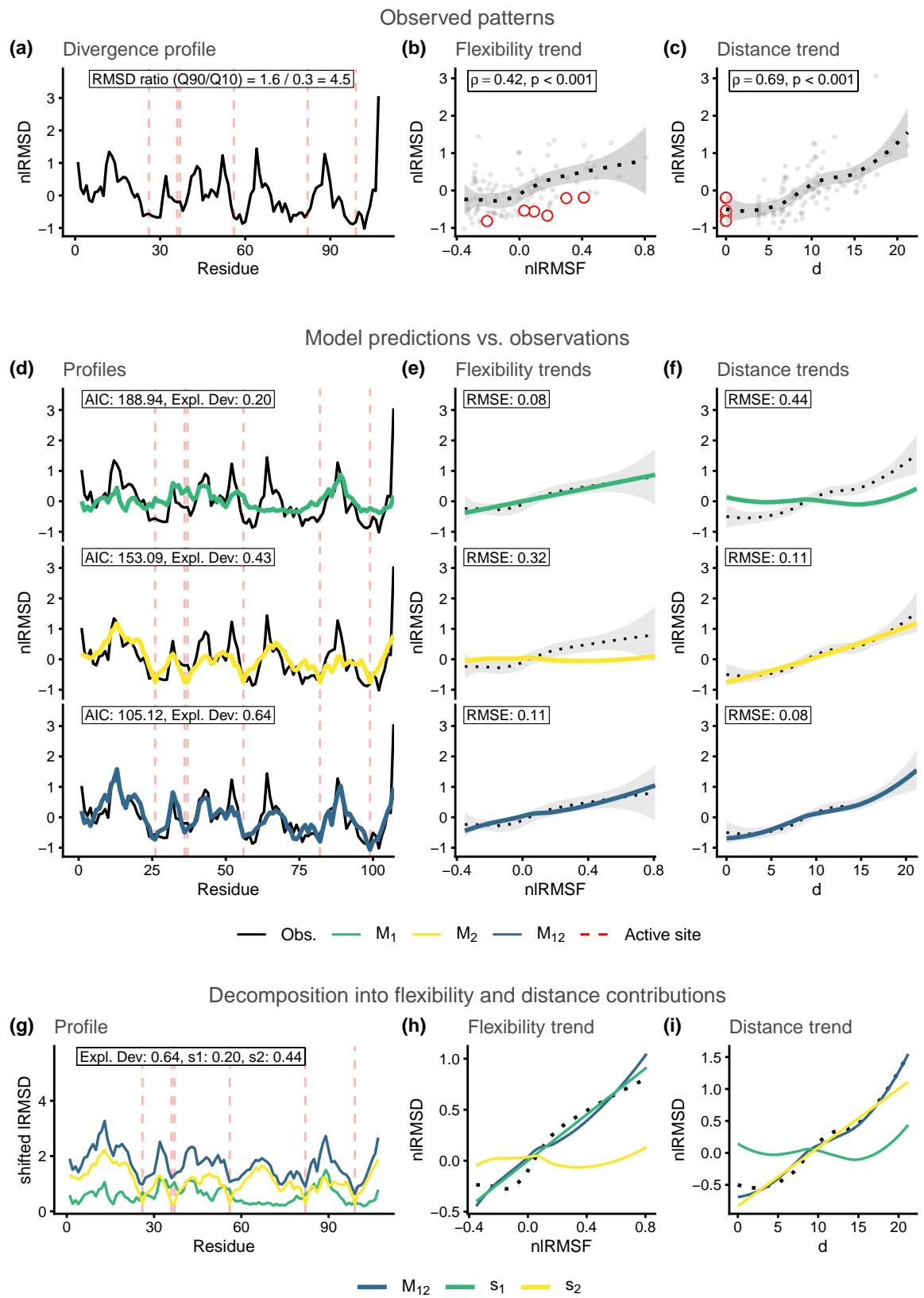


Figure S23: Structural divergence analysis for enzyme family MCSA ID: 362. Reference protein PDB ID: 1d6o_A.

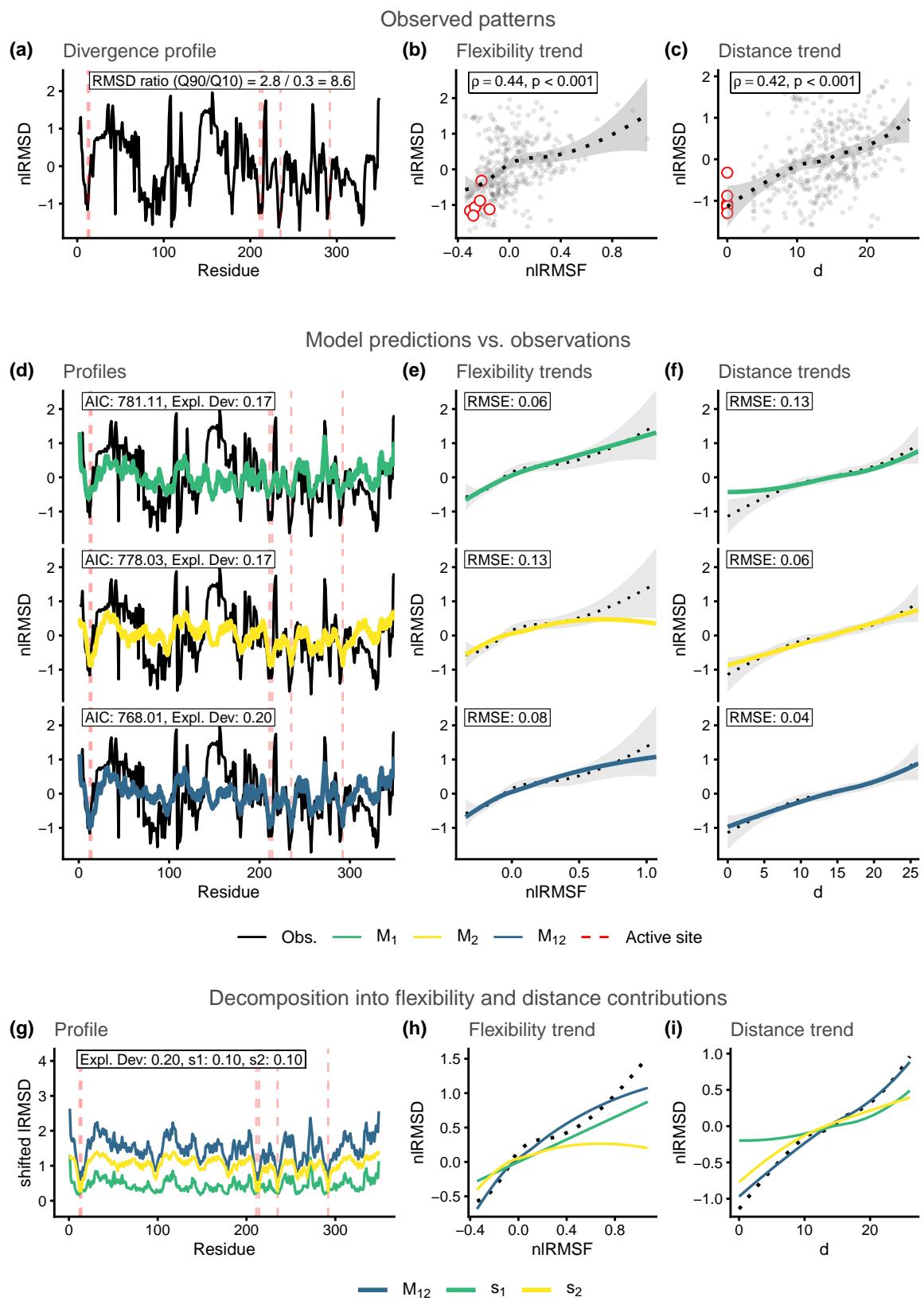


Figure S24: Structural divergence analysis for enzyme family MCSA ID: 376. Reference protein PDB ID: 1a4l_A.

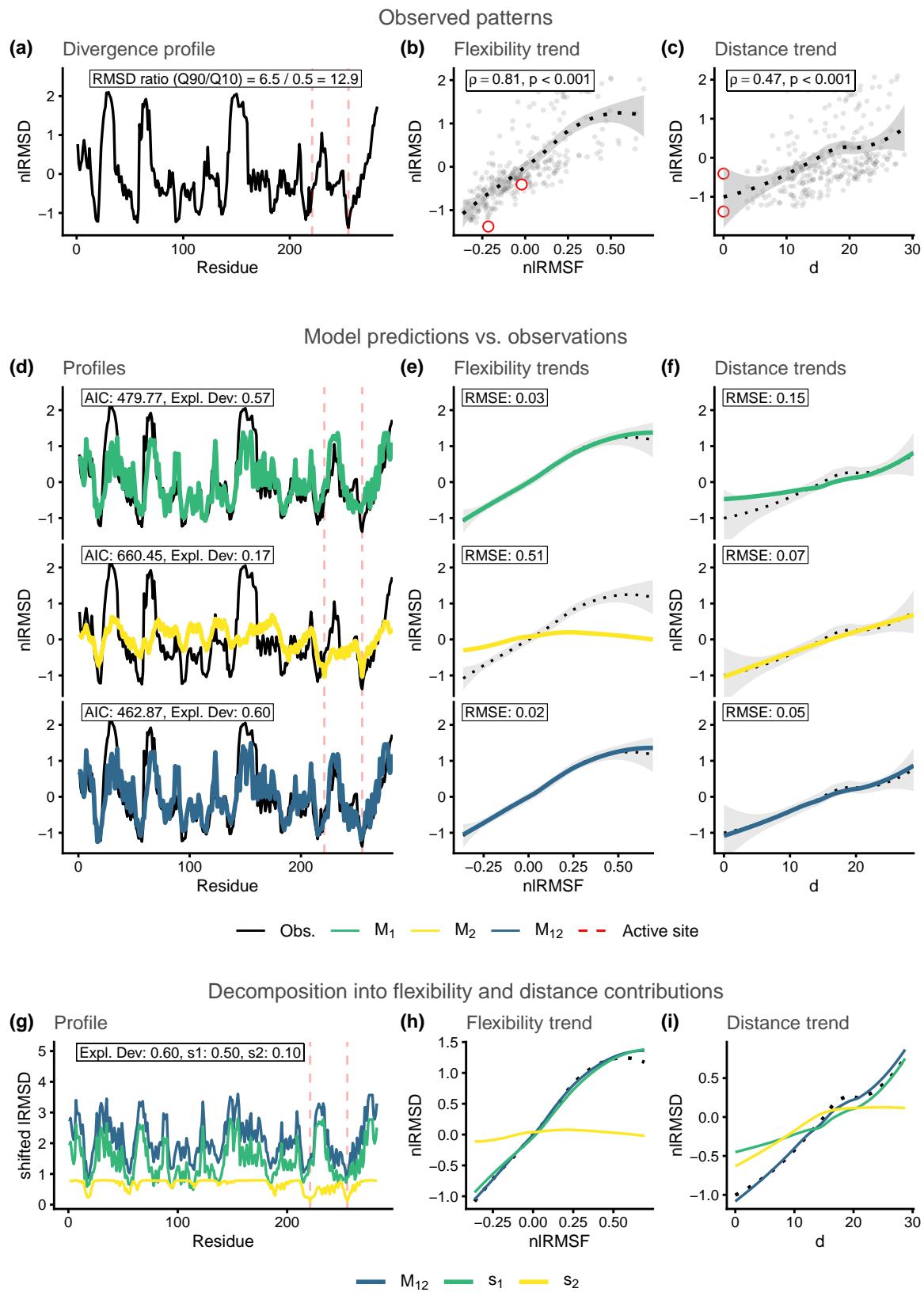


Figure S25: Structural divergence analysis for enzyme family MCSA ID: 394. Reference protein PDB ID: 1aj0_A.

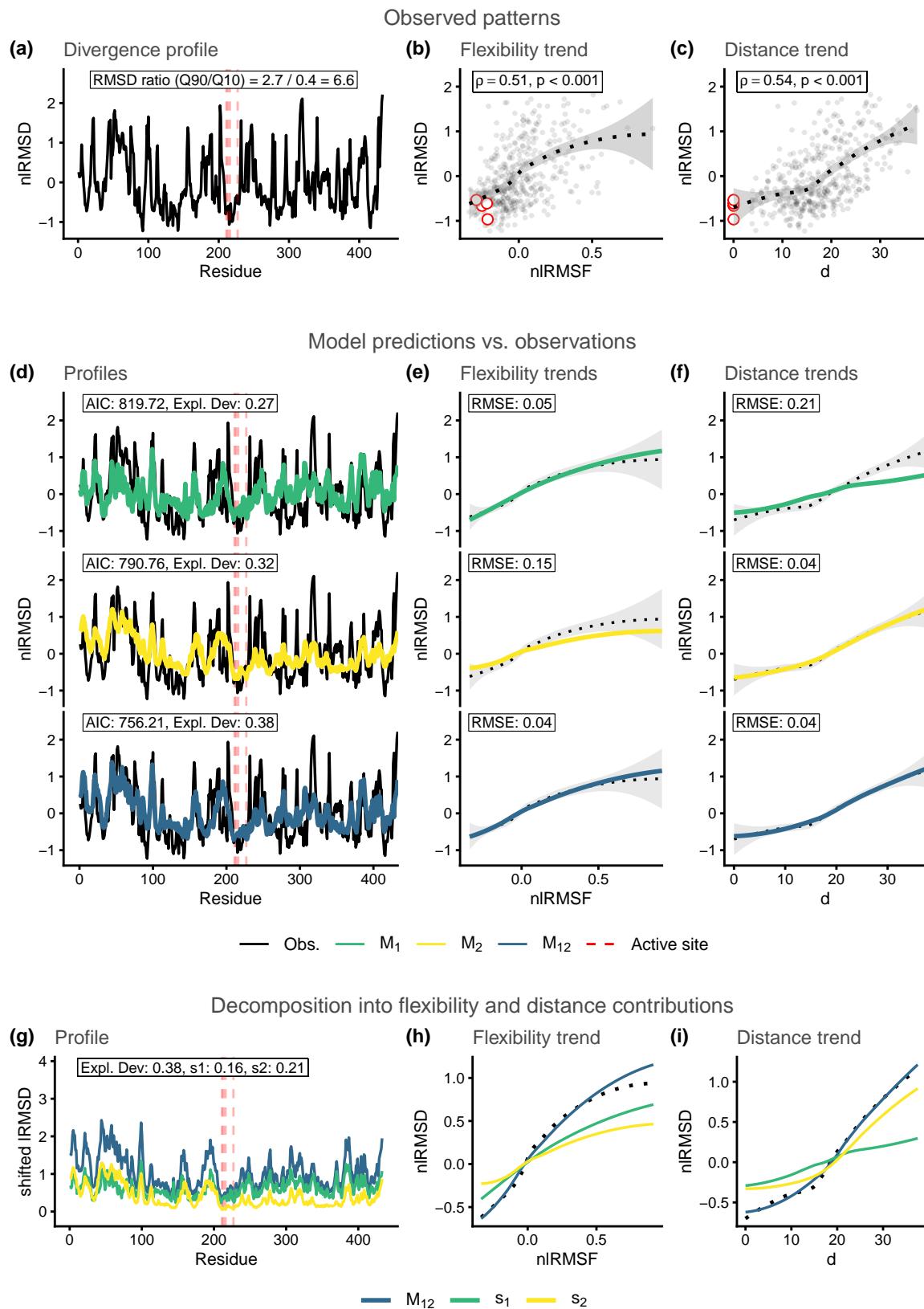


Figure S26: Structural divergence analysis for enzyme family MCSA ID: 444. Reference protein PDB ID: 1cel_A.

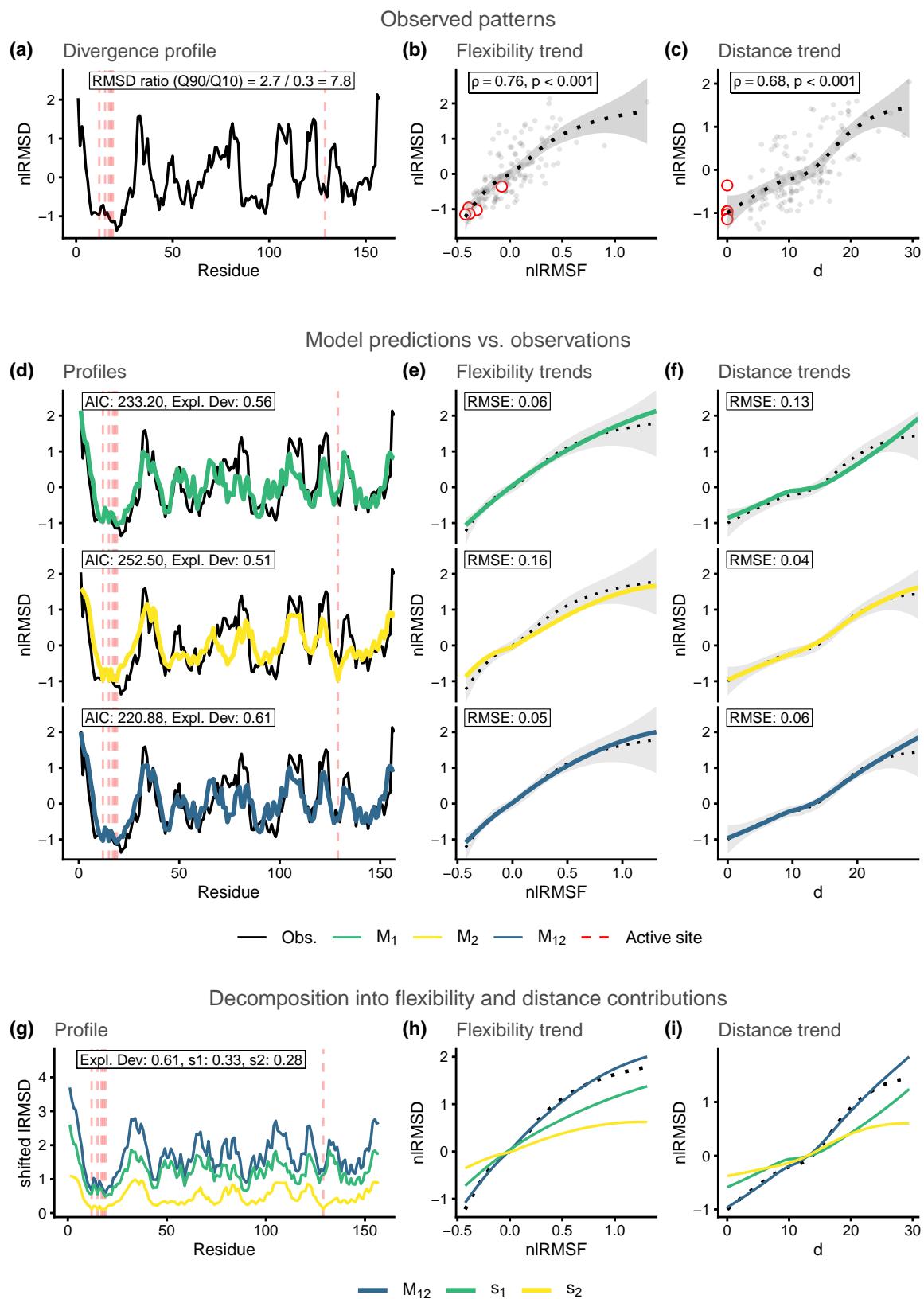


Figure S27: Structural divergence analysis for enzyme family MCSA ID: 462. Reference protein PDB ID: 1pnt_A.

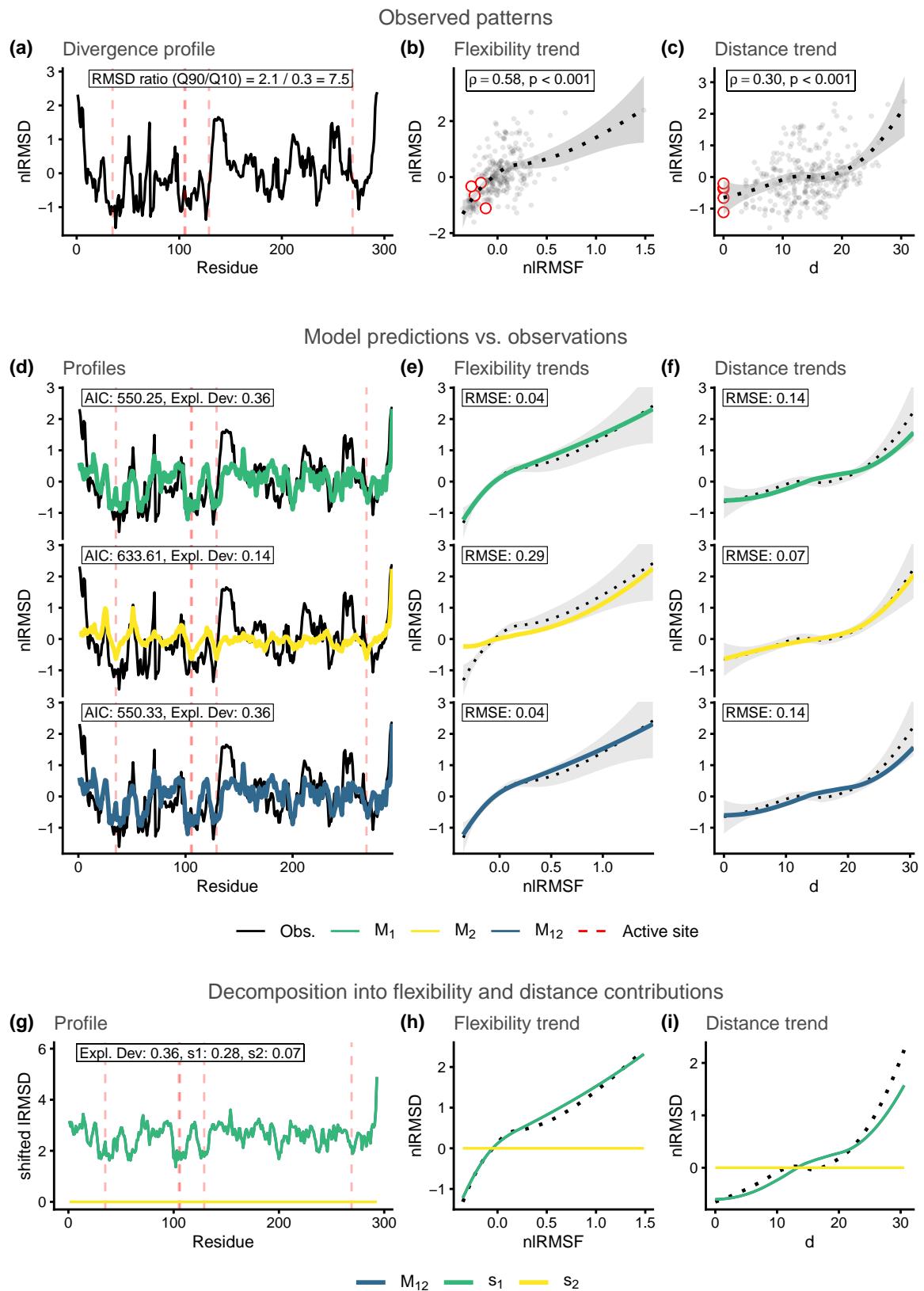


Figure S28: Structural divergence analysis for enzyme family MCSA ID: 467. Reference protein PDB ID: 1cv2_A.

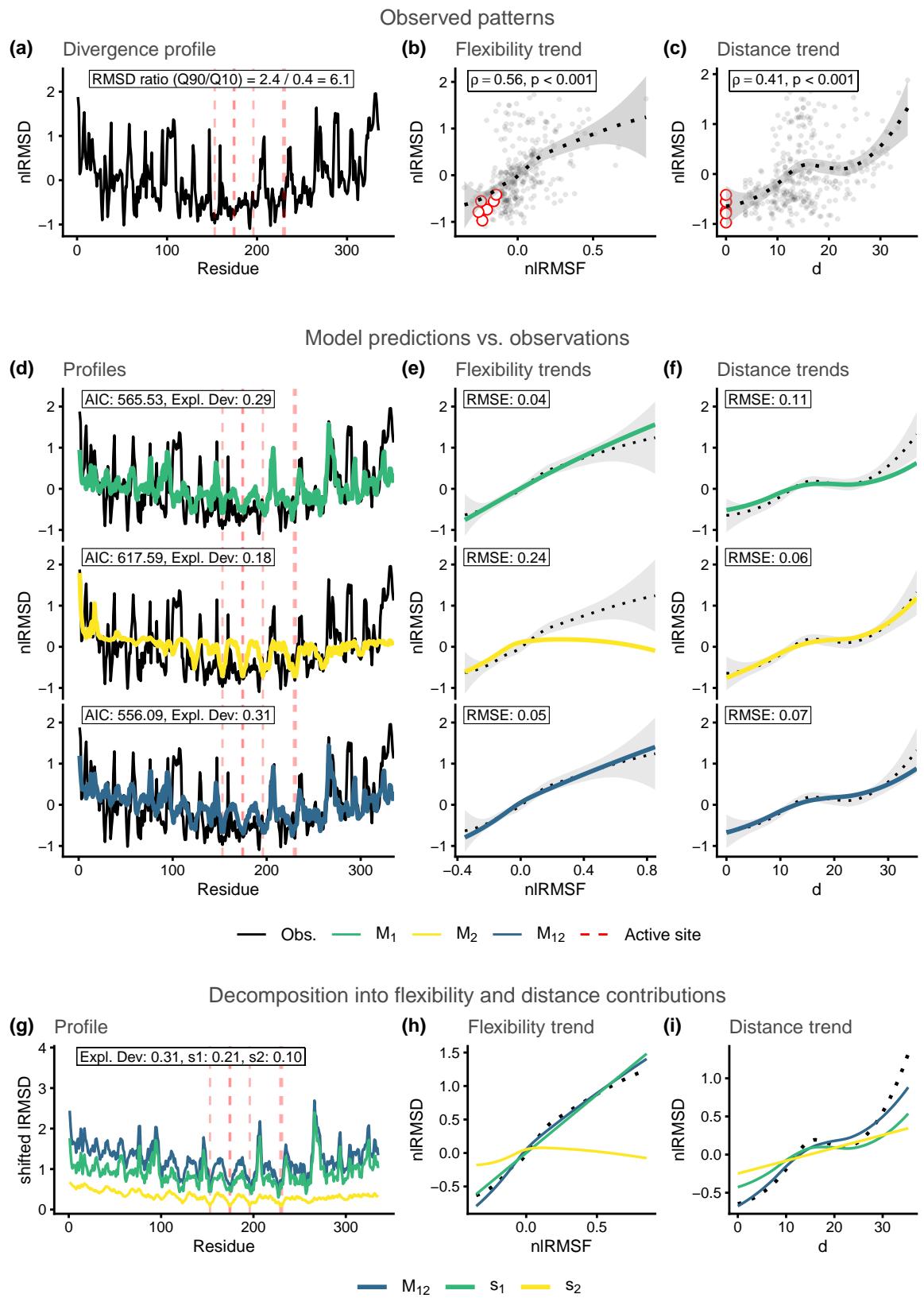


Figure S29: Structural divergence analysis for enzyme family MCSA ID: 480. Reference protein PDB ID: 1czf_A.

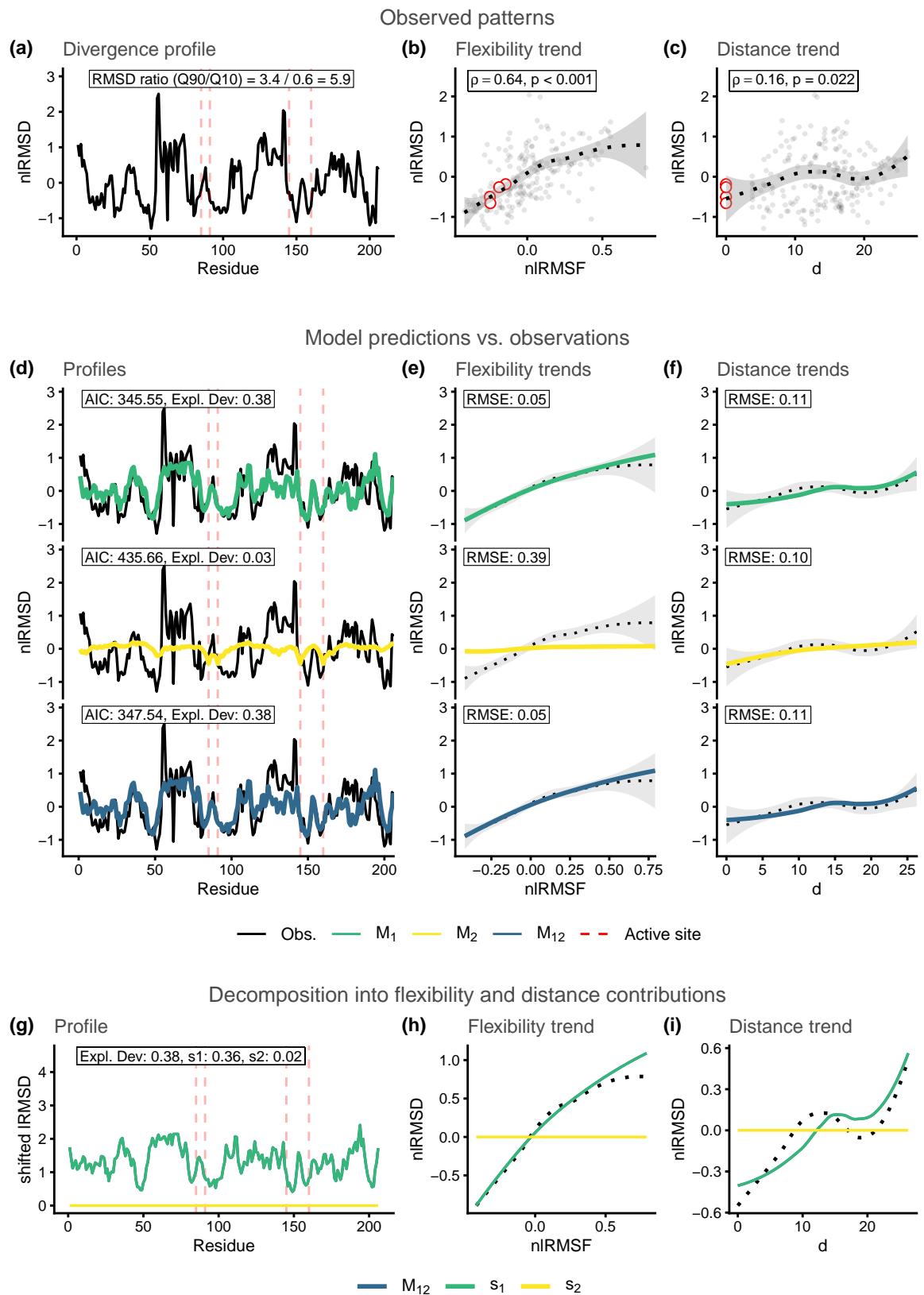


Figure S30: Structural divergence analysis for enzyme family MCSA ID: 597. Reference protein PDB ID: 1uch_A.

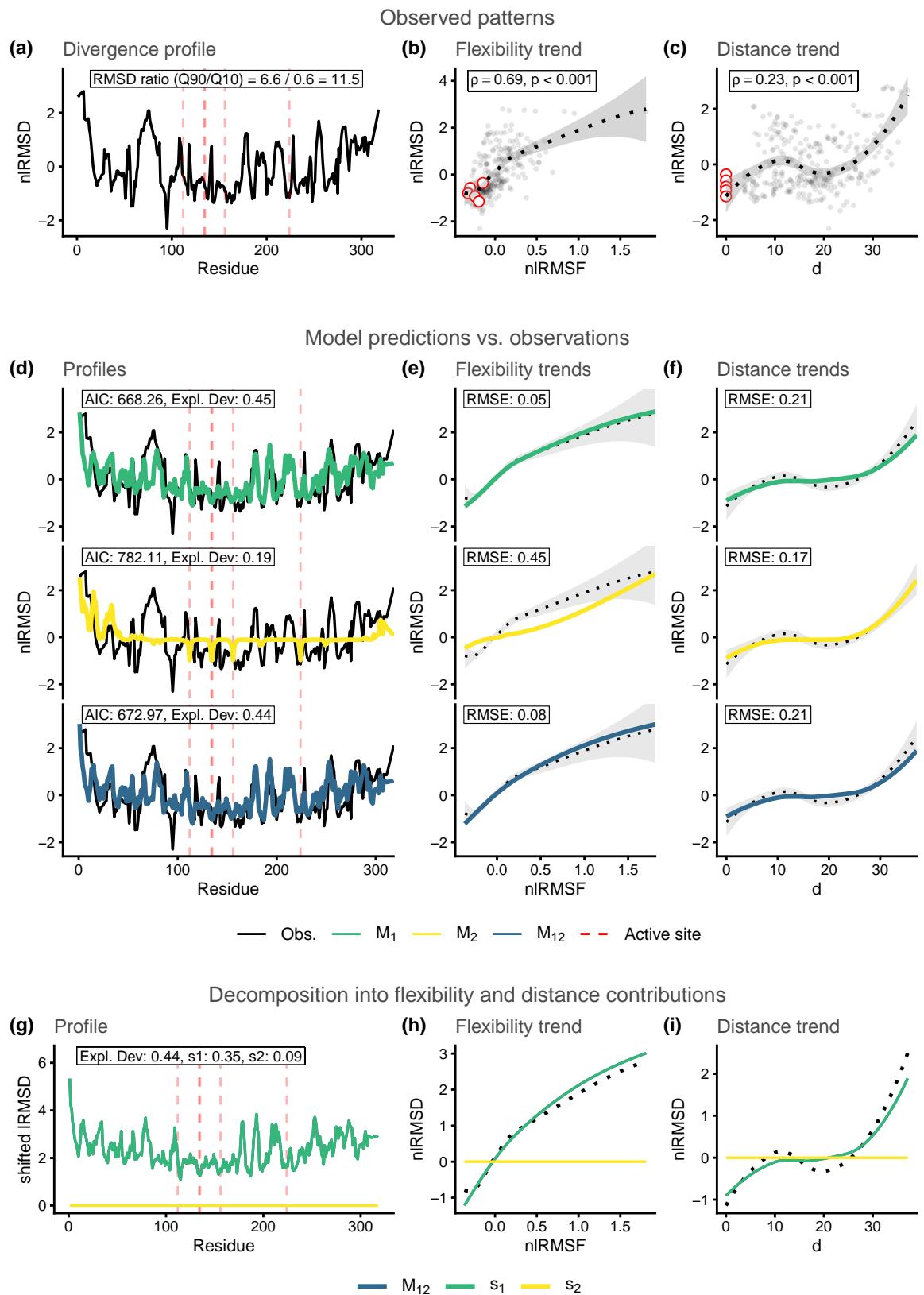


Figure S31: Structural divergence analysis for enzyme family MCSA ID: 681. Reference protein PDB ID: 1gq8_A.

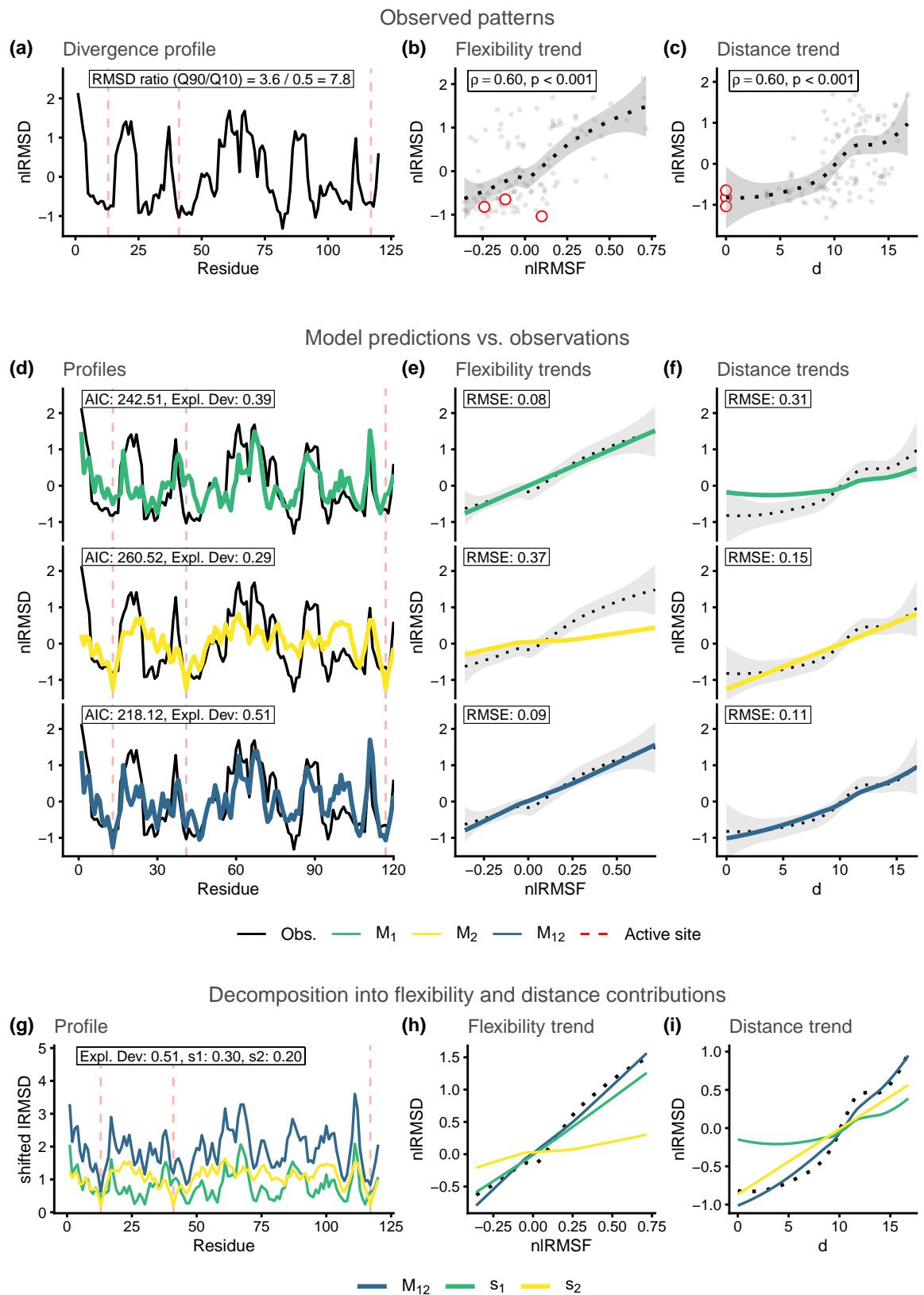


Figure S32: Structural divergence analysis for enzyme family MCSA ID: 693. Reference protein PDB ID: 2rnf_A.

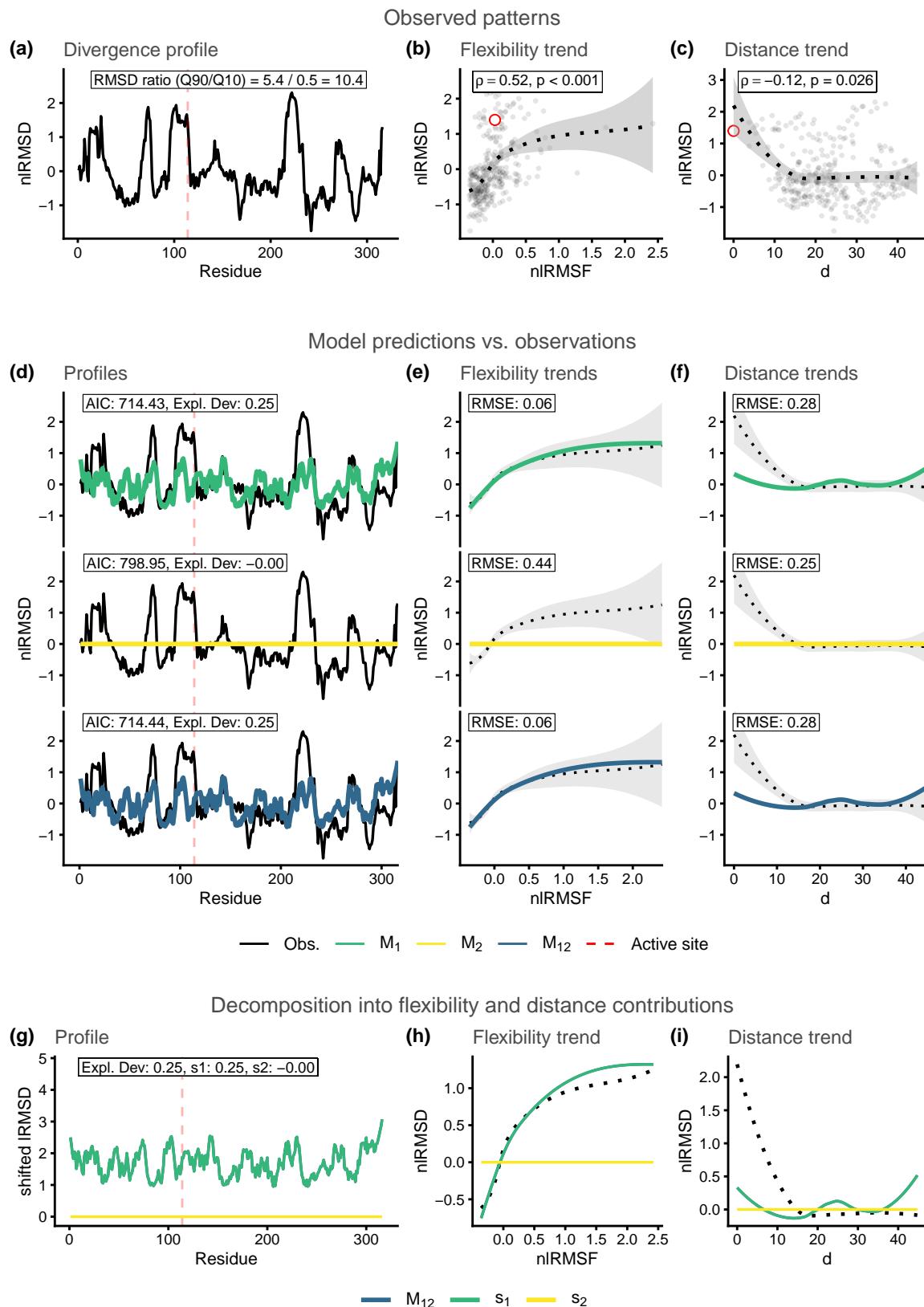


Figure S33: Structural divergence analysis for enzyme family MCSA ID: 749. Reference protein PDB ID: 1nml_A.

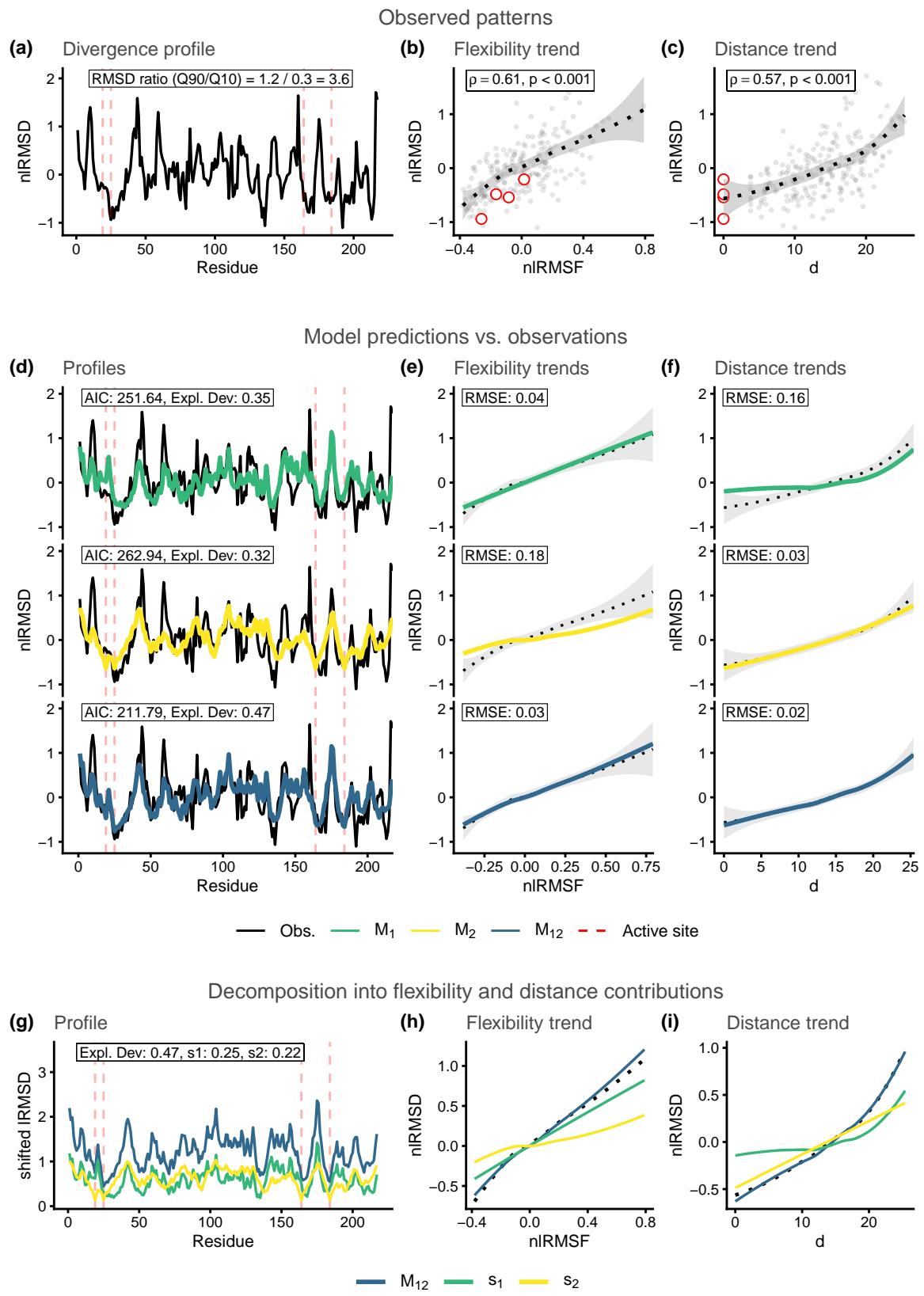


Figure S34: Structural divergence analysis for enzyme family MCSA ID: 814. Reference protein PDB ID: 1glo_A.

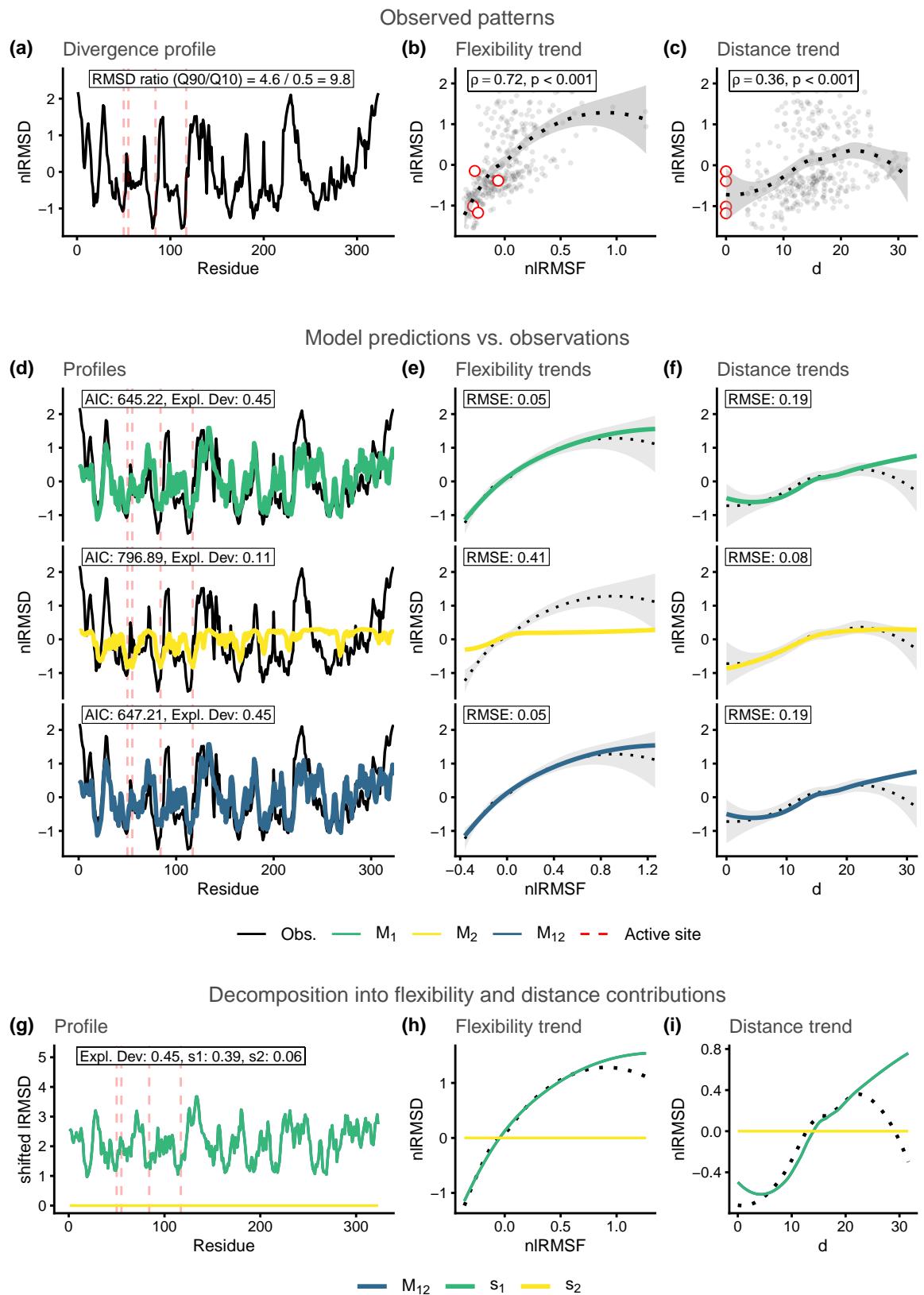


Figure S35: Structural divergence analysis for enzyme family MCSA ID: 858. Reference protein PDB ID: 1mraq_A.

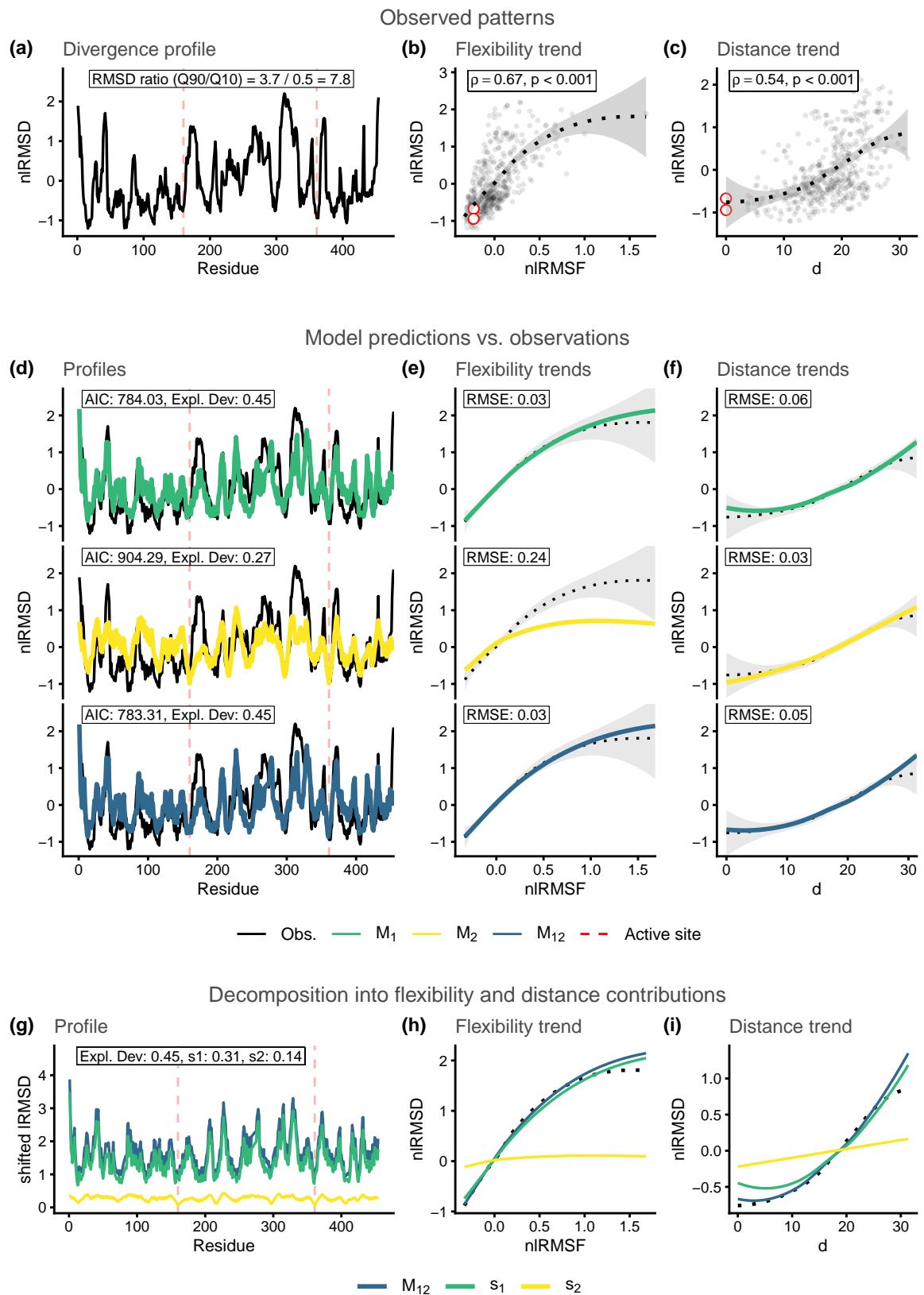


Figure S36: Structural divergence analysis for enzyme family MCSA ID: 877. Reference protein PDB ID: 1pbg_A.

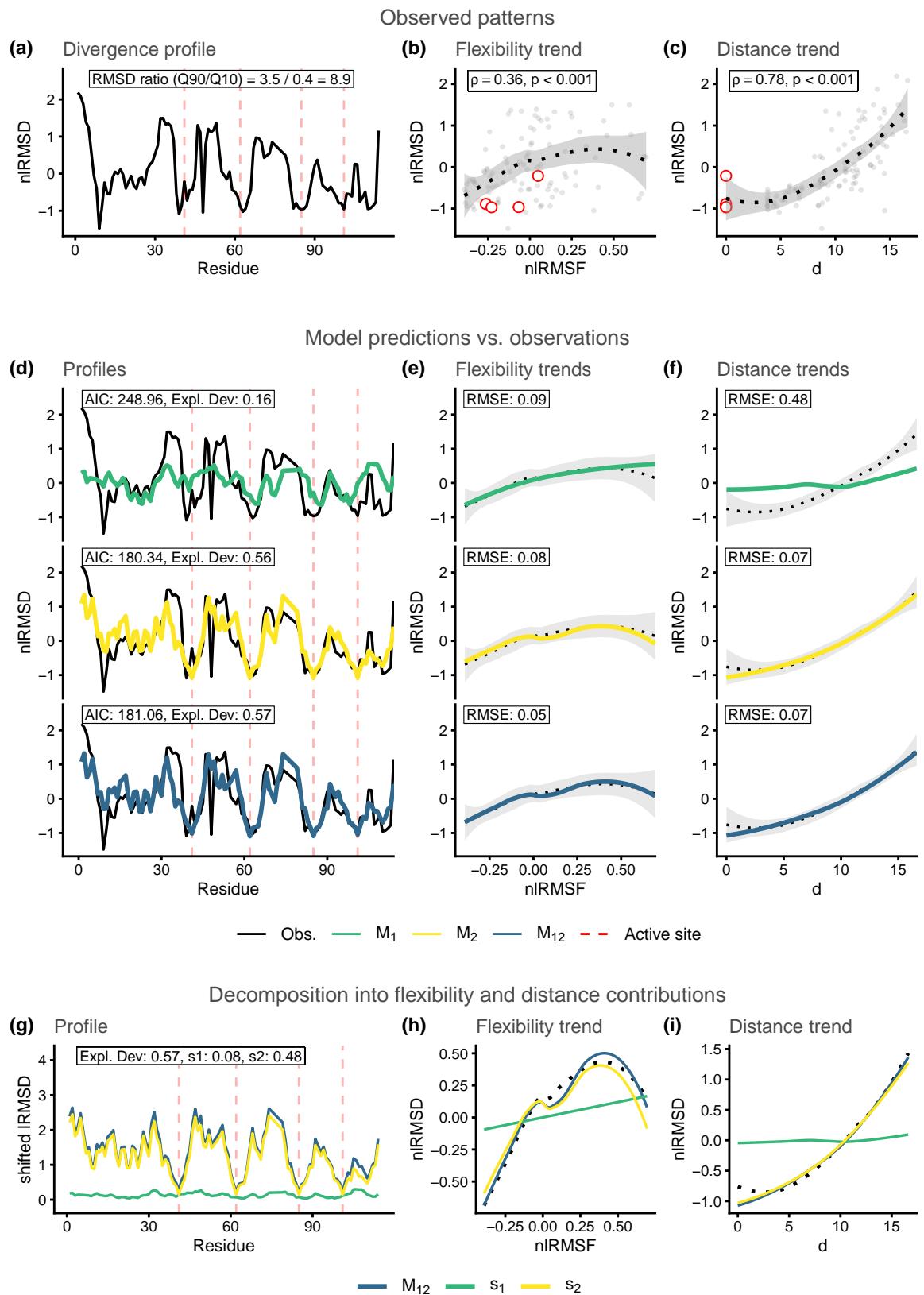


Figure S37: Structural divergence analysis for enzyme family MCSA ID: 908. Reference protein PDB ID: 1rtu_A.

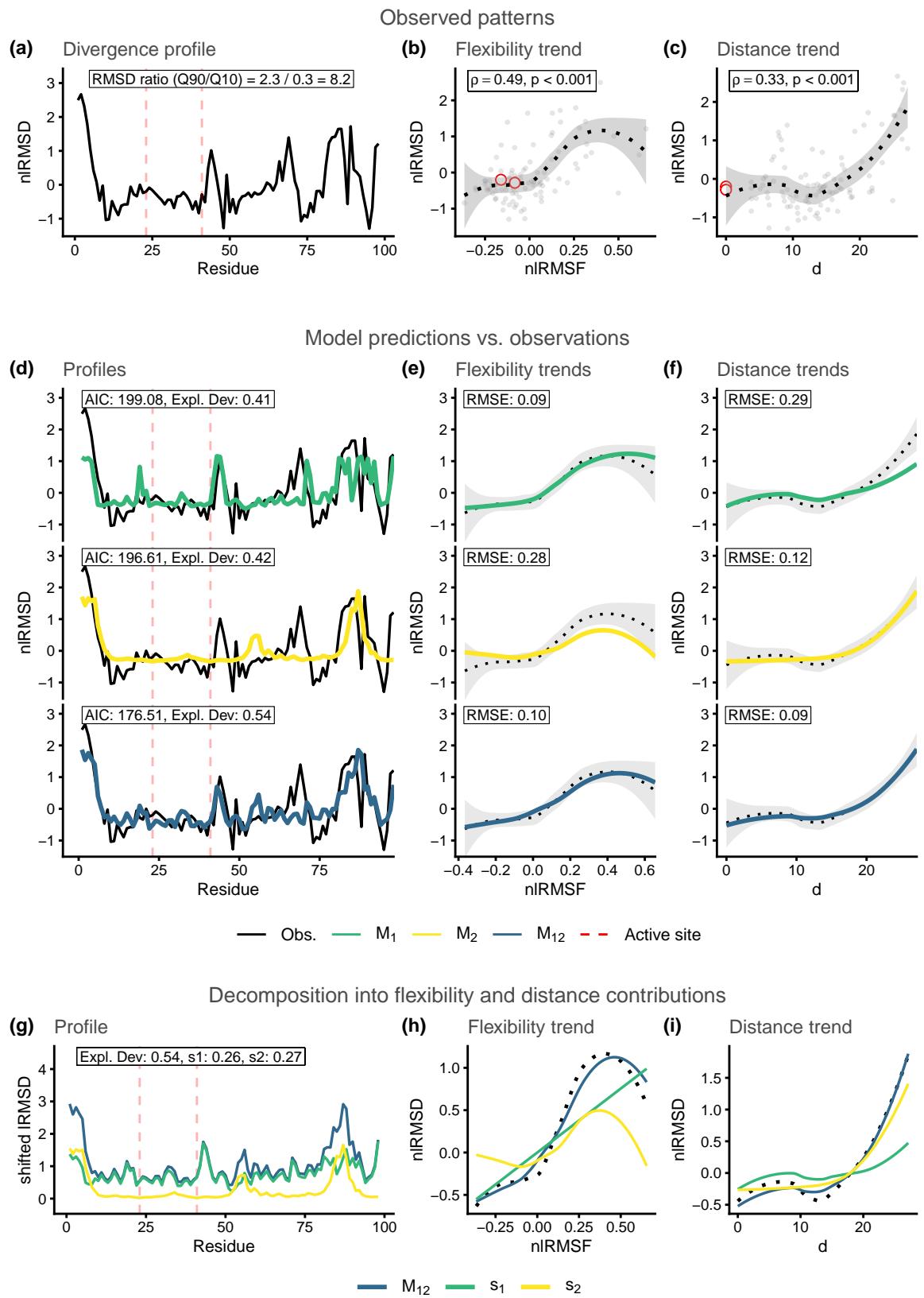


Figure S38: Structural divergence analysis for enzyme family MCSA ID: 923. Reference protein PDB ID: 2acy_A.

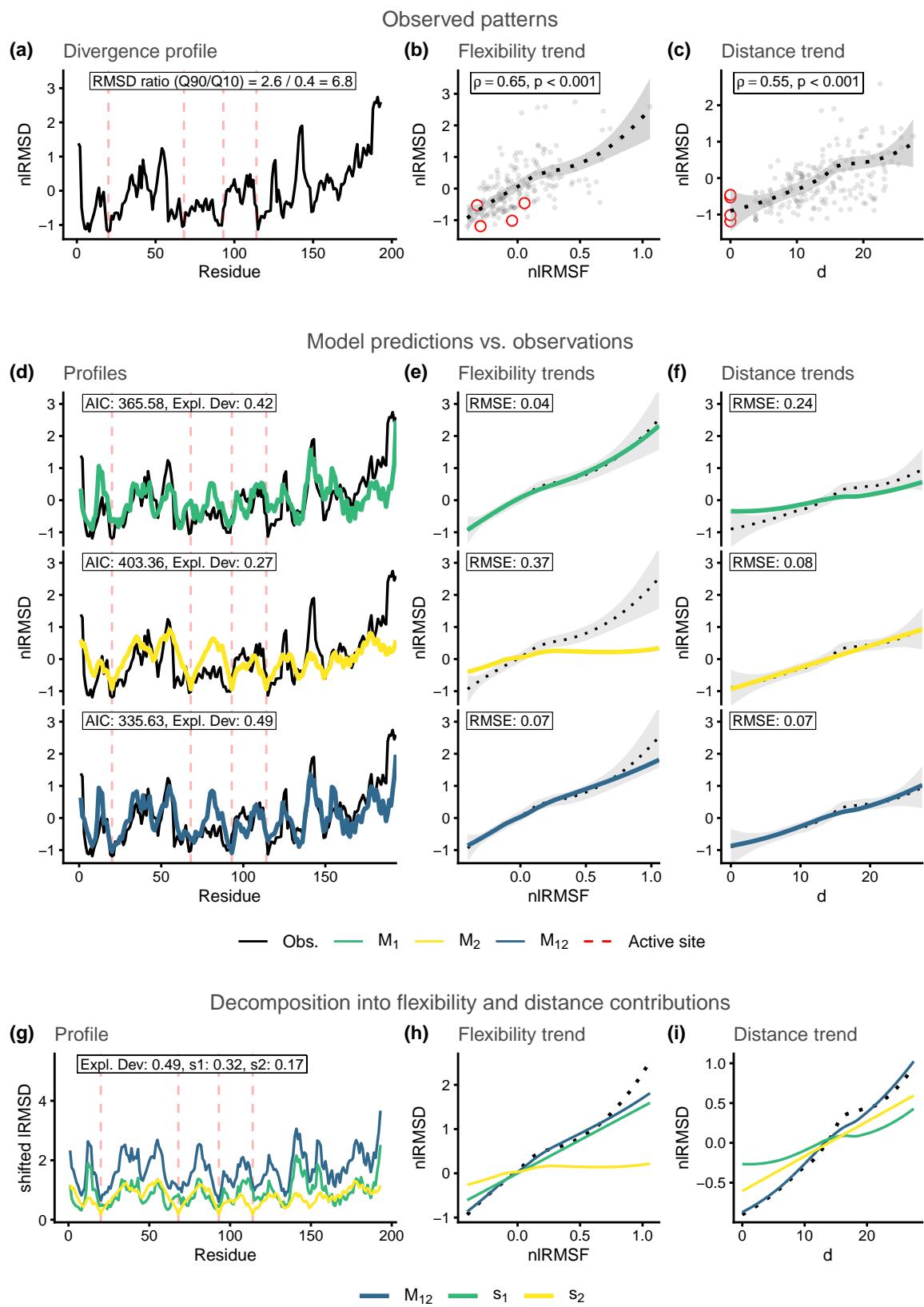


Figure S39: Structural divergence analysis for enzyme family MCSA ID: 931. Reference protein PDB ID: 2pth_A.