Supporting Information

pKAI: a fast and interpretable deep learning approach for accurate electrostatics-driven $\mathrm{p}K_\mathrm{a}$ predictions

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List of Figures

List of Tables

Results

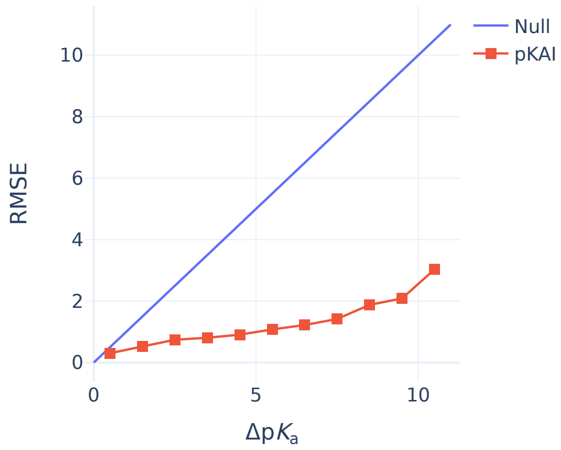
Table S1: Performance comparison between the Null model (RMSE) and pKAI (RMSE; percentage of errors below 0.5 pH units). Information about the distribution of residue pK_a shifts (ΔpK_a) and relative solvent accessible surface area (SASA$_r$) in the test data is also shown. The Null model was calculated with ΔpK_a equal to zero.

Residue	Abundance	Null	pKAI	Error	ΔpK_a		SASA$_r$	
	(%)	RMSE	RMSE	< 0.5 (%)	Avg	Stdev	Avg	Stdev
GLU	24.9	1.42	0.44	84.7	-0.7	1.2	0.43	0.24
LYS	22.5	1.04	0.32	92.1	0.6	0.9	0.47	0.23
ASP	21.9	1.74	0.50	80.5	-1.0	1.4	0.40	0.26
TYR	13.9	3.14	0.69	67.5	2.4	2.1	0.19	0.20
HIS	9.4	1.92	0.67	73.1	-1.0	1.6	0.29	0.25
CYS	3.9	3.30	0.82	56.6	2.8	1.8	0.11	0.17
NTR	1.7	0.74	0.28	94.2	-0.3	0.7	0.75	0.27
CTR	1.8	0.88	0.35	92.5	-0.2	0.9	0.74	0.27
All	100.0	1.89 (1.24^a)	0.52 (0.31^a)	81.2	0.0	1.9	0.38	0.27

[a] Mean Absolute Error (MAE)

Table S2: Execution time comparison between PypKa and pKAI. This benchmark was executed on a machine with a single Intel Xeon E5-2620 processor.

Protein	Number of residues / titratable	Execution Time (s)		Speedup Factor	Time per residue / titratable (s)	
		PypKa	pKAI		PypKa	pKAI
4LZT	129/21	26.5	0.8	33×	0.21/ 1.26	0.006/0.038
4K5C	341/100	92.0	1.2	76×	0.27/ 0.92	0.004/0.012
7C8J	902/249	2898.2	2.3	1260×	3.21/11.64	0.003/0.009



a)

Figure S1: RMSE variation versus the magnitude of the pK_a shift (ΔpK_a). The calculations were performed for pKAI and Null model using the PypKa predictions as reference.

Table S3: Experimental pK_a benchmark of several methods on a data set of 736 residues from 97 proteins. For each method, we report their RMSE, the mean absolute error (MAE), the 0.9 quantile, and the error percentage below 0.5 pK units. The null model values have been taken from.[1,2]

	RMSE	MAE	Quantile 0.9	Error < 0.5 (%)
Null	1.09	0.72	1.51	52.3
PypKA	1.07	0.71	1.48	52.6
PROPKA	1.11	0.73	1.58	51.1
pKAI	1.15	0.75	1.66	49.3
pKAI+	0.98	0.64	1.37	55.0

Table S4: Comparison between Null model and pKAI+ RMSE values. The Null model is defined as the pK_a values of the residues in water taken from Reference 1.

Residue	Abundance (%)	Null RMSE	pKAI+ RMSE	Error < 0.5 (%)	ΔpK_a		SASA$_r$	
					Avg	Stdev	Avg	Stdev
GLU	29.6	0.77	0.81	58.3	-0.5	0.9	0.45	0.24
LYS	14.4	0.74	0.68	60.4	0.3	0.6	0.55	0.21
ASP	29.2	1.30	1.08	59.5	-0.6	0.9	0.45	0.25
TYR	2.4	1.23	0.95	38.9	0.5	0.7	0.33	0.25
HIS	19.4	1.14	0.97	42.0	-0.5	1.1	0.39	0.22
CYS	1.2	3.39	3.43	0.0	-0.1	1.5	0.11	0.09
NTR	1.5	0.59	0.47	63.6	-0.3	0.8	0.74	0.20
CTR	2.2	0.41	0.56	75.0	-0.1	0.7	0.77	0.23
TOTAL	100.0	1.09	0.98	55.0	-0.4	1.0	0.46	0.25

[a] Mean Absolute Error (MAE)

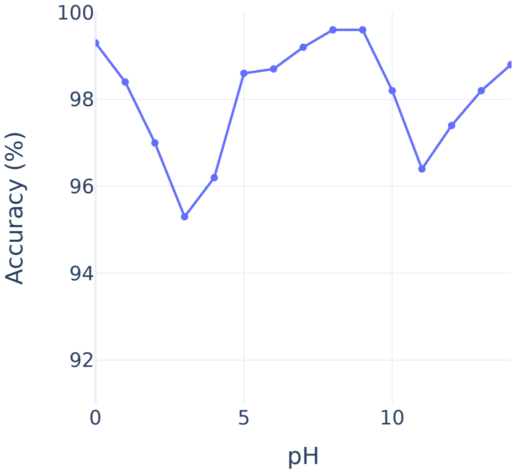


Figure S2: pKAI accuracy at predicting PypKa derived protonation states.

Table S5: One hot encoding classes of all atoms used.

Atom Name	Residue	Atom Classes
N	Main Chain	N
O	Main Chain	O
NE2	GLN	N_AMIDE
ND2	ASN	N_AMIDE
OE1	GLN	O_AMIDE
OD1	ASN	O_AMIDE
NE	ARG	NE_ARG
NH1/NH2	ARG	NH_ARG
NZ	LYS	NZ_LYS
N	NTR	NZ_LYS
OXT	CTR	O_COOH
OD1/OD2	ASP	O_COOH
OE1/OE2	GLU	O_COOH
OG	SER	OG_SER
OG1	THR	OG1_THR
ND1	HIS	ND1_HIS
NE2	HIS	NE2_HIS
NE1	TRP	NE1_TRP
OH	TYR	OH_TYR
SG	CYS	SG_CYS
SD	Methionine	SD_MET

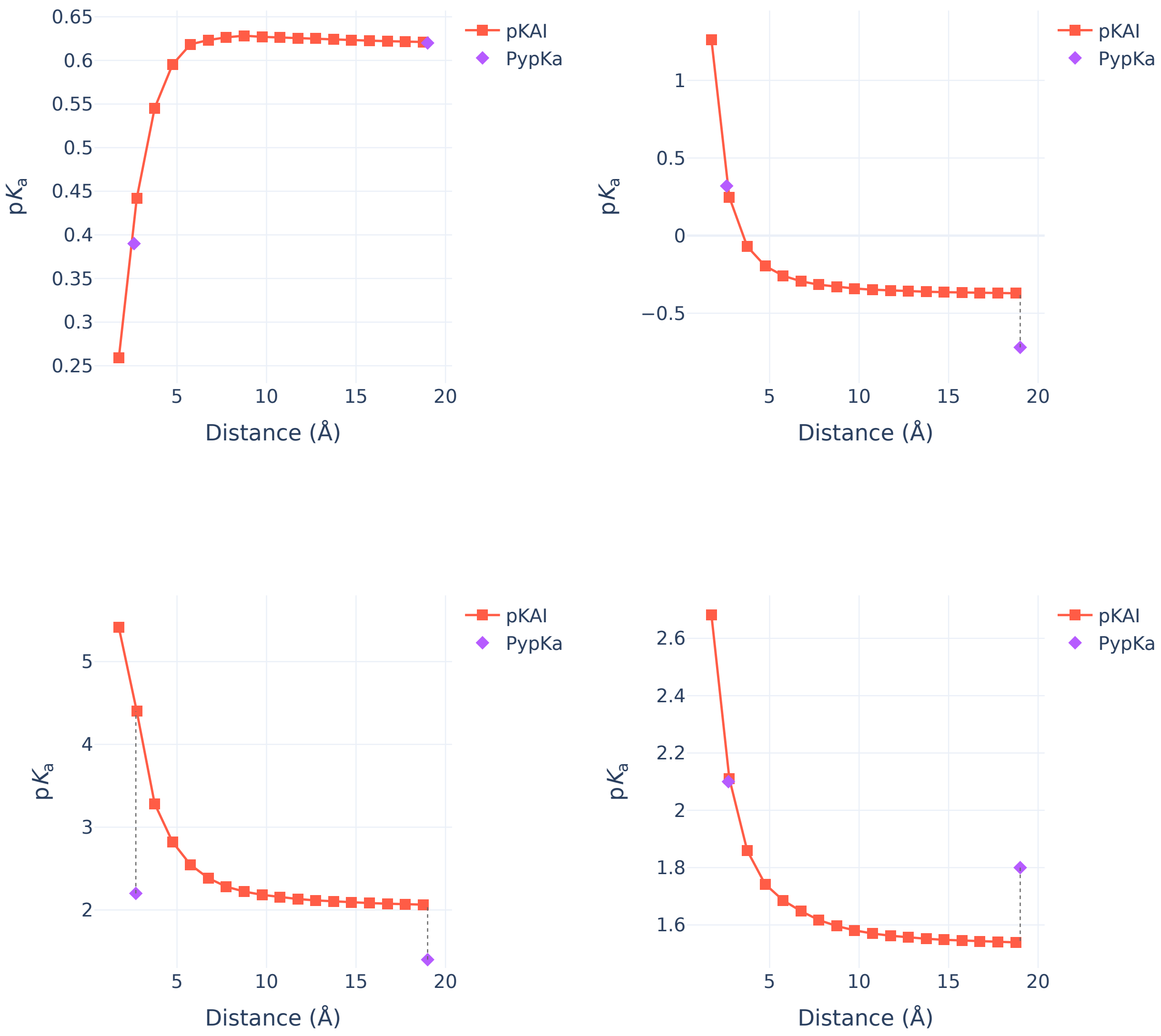


Figure S3: Impact of changing the distance of the closest atom on pKAI's predictions for: residue GLU-154 from structure 6FT4 (A); residue LYS-118 from structure 2HRK (C); residue TYR-98 from structure 6FT4 (C); residue LYS-55 from structure 2BJU (D). For reference, we have included PypKa's predictions of the same residue in the state presented in the experimental structure and in an modified structure in which the closest atom is absent.

References

(1) Thurlkill, R. L.; Grimsley, G. R.; Scholtz, J. M.; Pace, C. N. pK values of the ionizable groups of proteins. *Protein Sci.* **2006**, *15*, 1214–1218.

(2) Grimsley, G. R.; Scholtz, J. M.; Pace, C. N. A summary of the measured pK values of the ionizable groups in folded proteins. *Protein Sci.* **2009**, *18*, 247–251.