Supplementary Materials

Exploring the solubility limits of Edaravone in neat solvents and binary mixtures: experimental and machine learning study

Maciej Przybyłek, Tomasz Jeliński, Magdalena Mianowana, Kinga Misiak, Piotr Cysewski
Department of Physical Chemistry, Pharmacy Faculty, Collegium Medicum of Bydgoszcz, Nicolaus Copernicus University in Toruń, Kurpińskiego 5, 85-096 Bydgoszcz, Poland

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S1. New edaravone solubility data

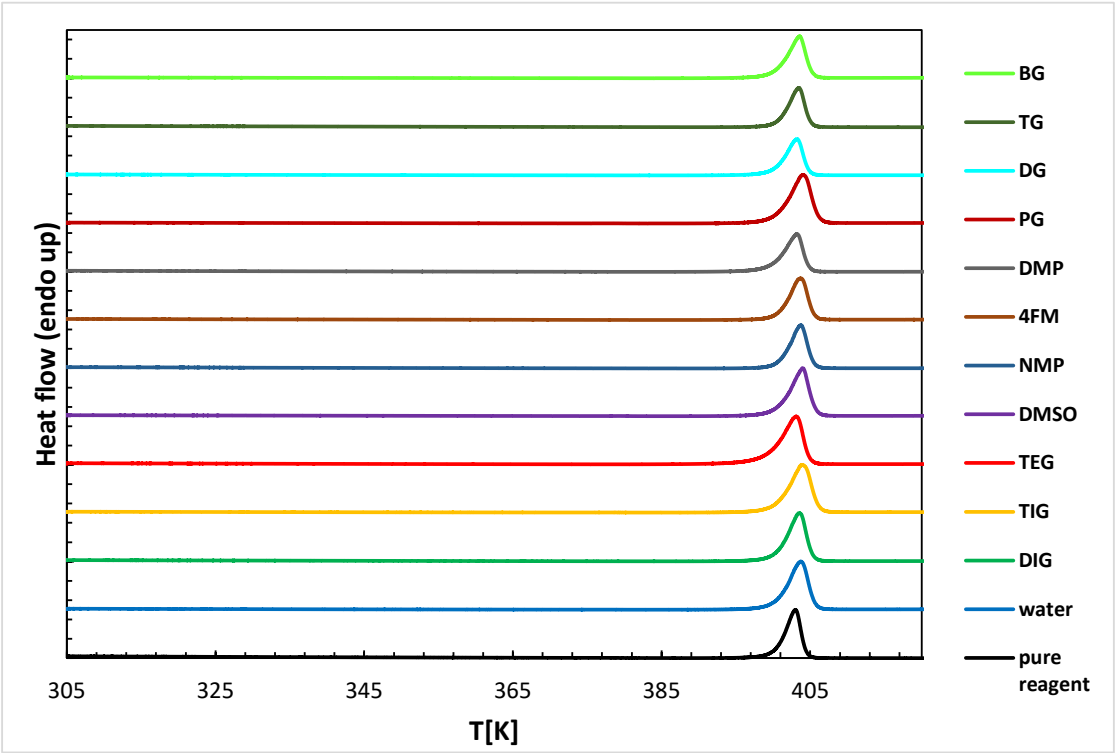
Table S1.1. The experimentally determined mole fraction solubility of Edaravone (x_{EDA}, $\cdot 10^2$) in diglyme (DIG), triglyme (TIG), tetraglyme (TEG), dimethyl sulfoxide (DMSO), 1-methyl-2-pyrrolidone, (NMP), 4-formylmorpholine (4FM), and 2,4-dimethylphenol (DMP) at various temperatures. Standard deviation values are given in parentheses.

solvent	Edaravone solubility (x_{EDA}, $\cdot 10^2$)			
	25 °C	30 °C	35 °C	40 °C
DMSO	7.58 (±0.32)	12.25 (±0.16)	20.1 (±0.15)	29.81 (±1.14)
TEG	4.63 (±0.05)	8.63 (±0.22)	13.05 (±0.19)	21.21 (±0.64)
NMP	3.83 (±0.01)	4.96 (±0.49)	6.94 (±0.19)	8.61 (±0.21)
DIG	2.05 (±0.02)	2.69 (±0.04)	3.33 (±0.11)	4.16 (±0.06)
DMP	1.88 (±0.05)	2.82 (±0.58)	4.08 (±0.21)	5.65 (±0.25)
TIG	1.53 (±0.07)	2.20 (±0.04)	3.11 (±0.17)	4.57 (±0.39)
4FM	1.11 (±0.01)	1.46 (±0.08)	1.76 (±0.19)	2.17 (±0.01)

Table S1.2. The experimentally determined mole fraction solubility of Edaravone (x_{EDA}, $\cdot 10^2$) in 1,2-propanediol (PG), diethylene glycol (DG), triethylene glycol (TG), and 1,3-butanediol (BG), as well as in their aqueous binary mixtures at 25 °C. In the first column, x_2* denotes the mole fraction of the organic solvent in solute-free solutions. Standard deviation values are given in parentheses.

x_2*	Edaravone solubility (x_{EDA}, $\cdot 10^2$)			
	PG	DG	TG	BG
0.0	0.02 (<±0.01)	0.02 (<±0.01)	0.02 (<±0.01)	0.02 (<±0.01)
0.1	0.06 (±0.01)	0.09 (±0.01)	0.31 (±0.04)	0.12 (±0.02)
0.2	0.15 (±0.01)	0.25 (±0.01)	0.78 (±0.03)	0.29 (±0.04)
0.3	0.26 (±0.02)	0.48 (±0.04)	1.28 (±0.07)	0.53 (±0.03)
0.4	0.40 (±0.02)	0.74 (±0.03)	1.72 (±0.06)	0.83 (±0.04)
0.5	0.54 (±0.02)	1.09 (±0.01)	2.11 (±0.08)	1.07 (±0.05)
0.6	0.71 (±0.02)	1.39 (±0.02)	2.54 (±0.08)	1.27 (±0.03)
0.7	0.86 (±0.02)	1.65 (±0.05)	3.03 (±0.09)	1.42 (±0.05)
0.8	0.99 (±0.02)	1.87 (±0.04)	3.51 (±0.09)	1.50 (±0.03)
0.9	1.00 (±0.02)	1.98 (±0.02)	3.58 (±0.06)	1.51 (±0.04)
1.0	0.85 (±0.01)	2.04 (±0.06)	2.75 (±0.08)	1.43 (±0.04)

A



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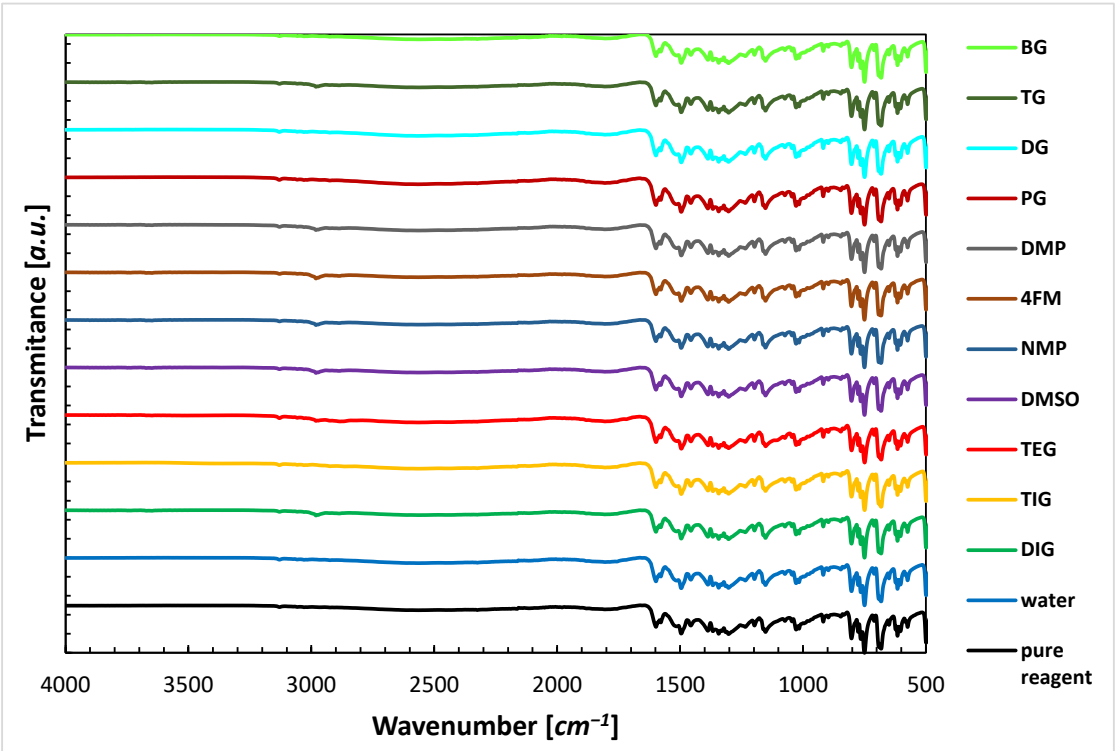


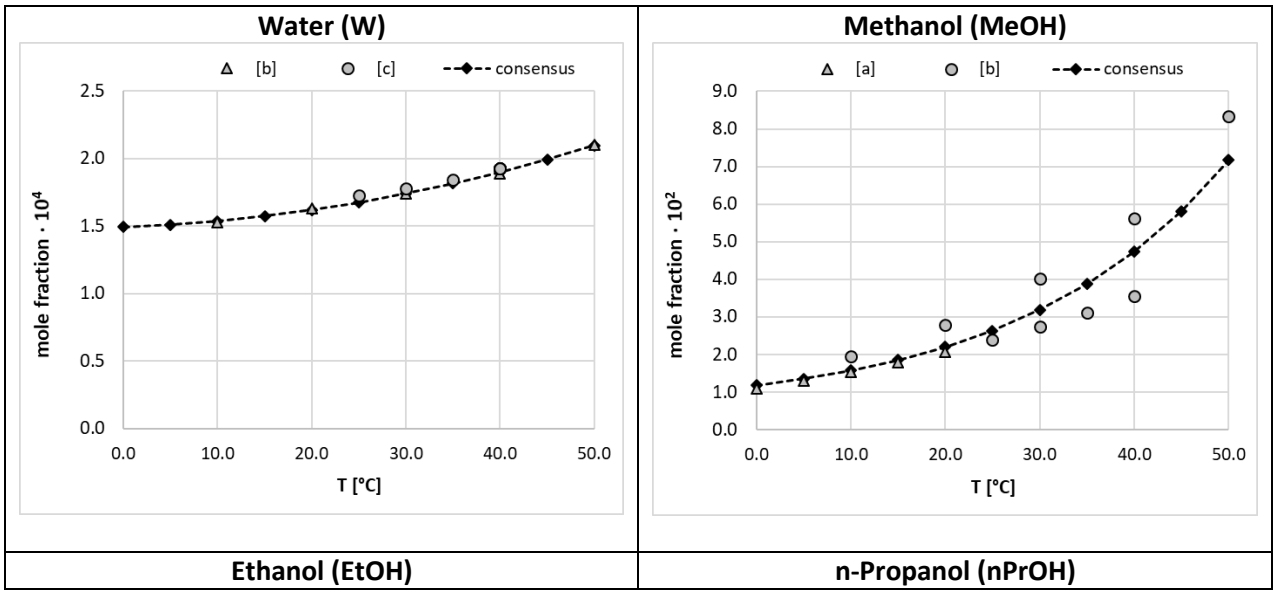
Figure S1.3. The DSC (A) and FTIR-ATR (B) characteristics of the solid residues obtained after shake-flask solubility determination procedure. Notation is the same as in Table S1.1. and S1.2.

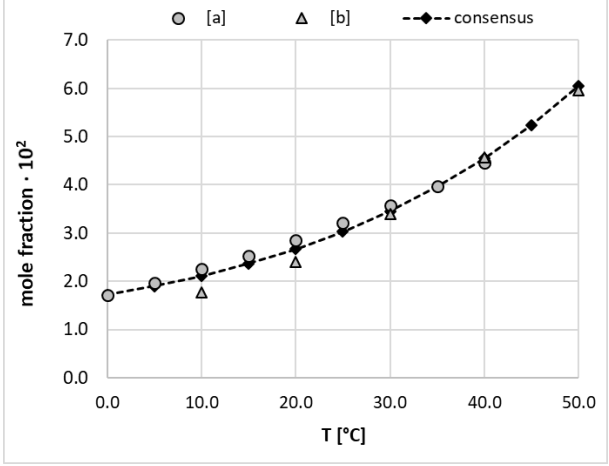
S2. Solubility data curation

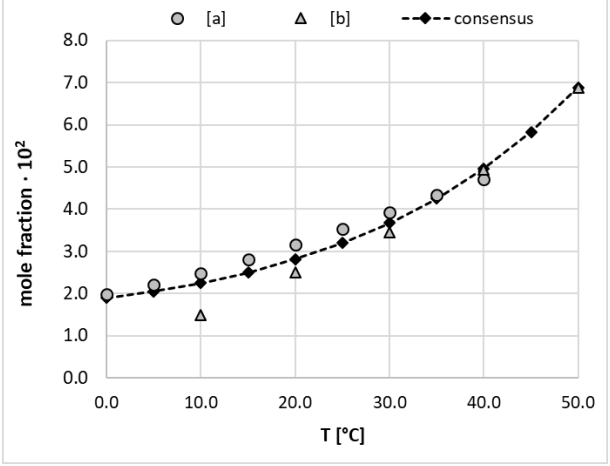
S2.1. Collection of EDA solubility in neat solvents

Table S2.1. Optimized values of model parameters used for data curation along with statistical measure of the fitting accuracy.

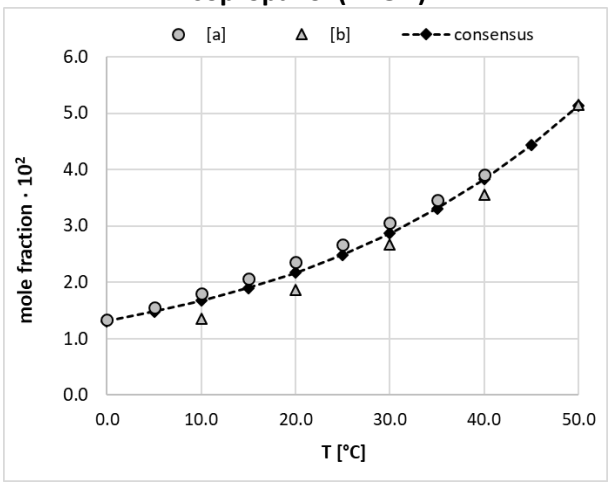
solvent	acronim	A·10³	B·10³	C·10³	RMSD·10³	MAPE
water	W	3.111	-6.398	0.858	4.03	0.04
methanol	MeOH	31.984	-17.949	2.185	165.47	4.19
ethanol	EtOH	20.389	-11.949	1.439	68.09	1.33
n-propanol	nPrOH	29.274	-17.128	2.198	133.95	2.51
isopropanol	iPrOH	18.599	-10.825	1.246	90.26	1.90
n-butanol	nBuOH	15.486	-8.444	0.834	8.89	0.24
isobutanol	iBuOH	21.045	-11.898	1.348	18.43	0.45
sec-butanol	sBuOH	20.873	-11.790	1.332	11.53	0.30
n-pentanol	nPeOH	34.206	-20.257	2.695	14.61	0.34
acetone	AT	49.838	-28.045	3.600	192.27	4.65
acetonitrile	AE	8.189	-3.658	0.000	58.89	1.22
dichloromethane	DC	40.161	-22.691	2.956	11.54	0.36
ethyl acetate	EA	44.601	-26.411	3.577	178.67	4.16
1,4-dioxane	D	17.497	-9.079	0.865	21.92	0.68
toluene	T	3.251	-1.145	-0.296	7.08	0.16
2,4-dimethylphenol	DMP	-16.508	14.856	-3.315	3.76	0.10
1-methyl-2-pyrrolidone	NMP	10.517	-3.004	-0.330	23.14	0.73
diglyme	DIG	-12.269	9.697	-2.146	7.41	0.18
triglyme	TIG	62.116	-33.404	4.066	5.93	0.14
tetraglyme	TEG	-31.442	27.130	-5.565	32.42	1.16
DMSO	DMSO	-9.106	13.021	-3.302	14.09	0.74
4FM	4FM	9.308	-4.112	0.000	15.91	0.31



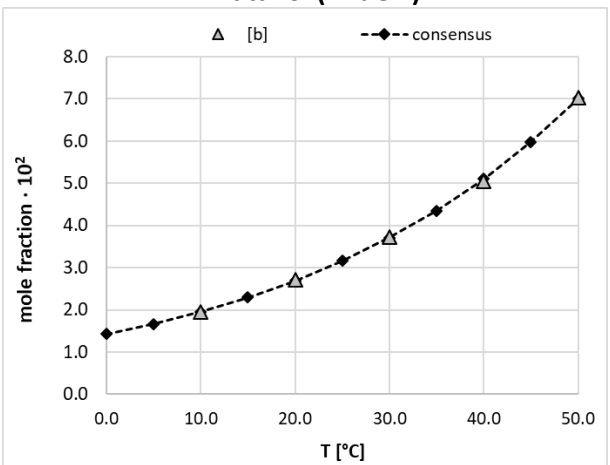




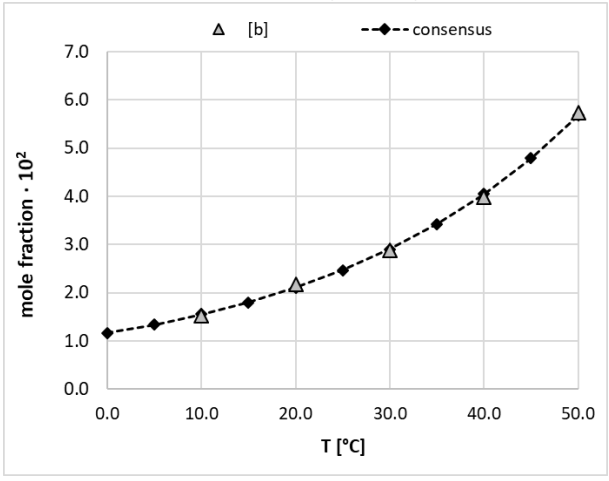
Isopropanol (iPrOH)



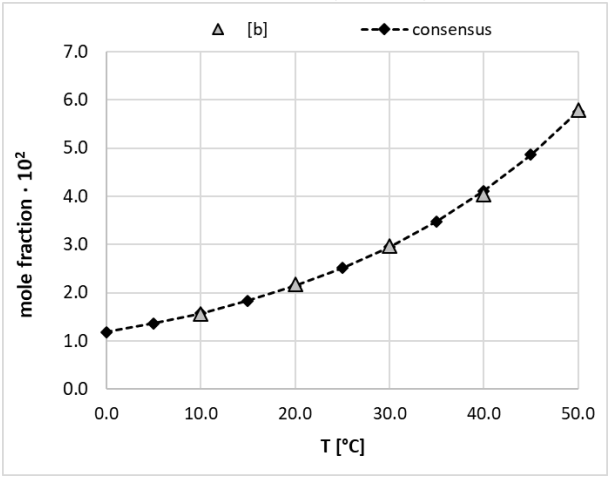
n-Butanol (nBuOH)



Isobutanol (iBuOH)

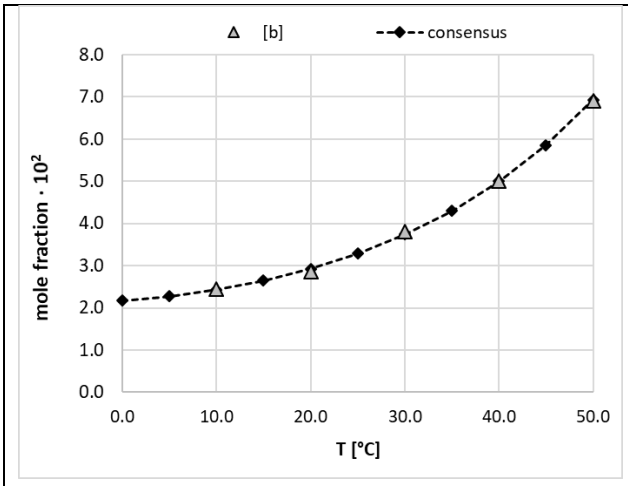


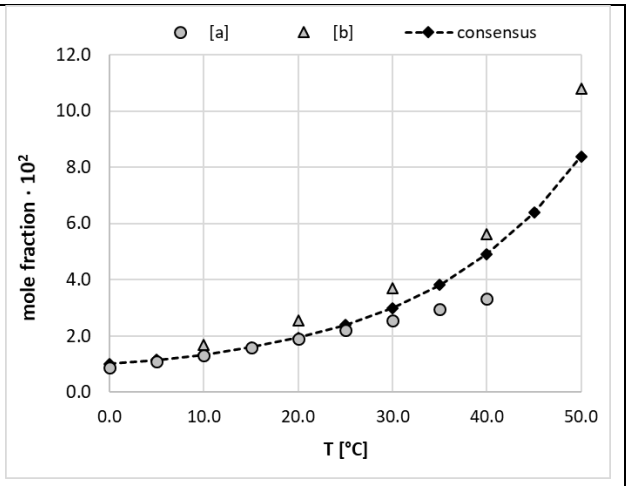
sec-Butanol (sBuOH)



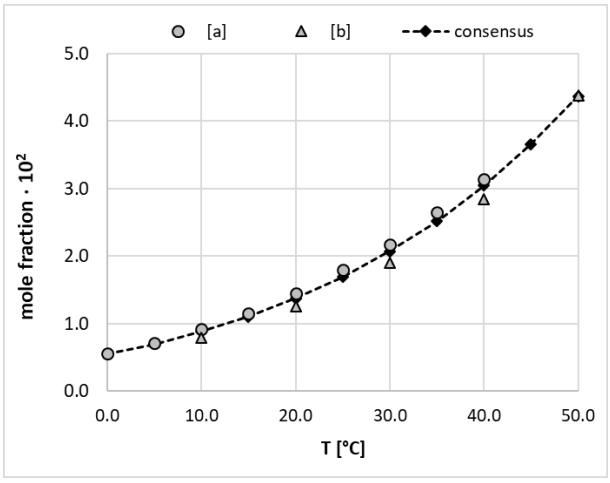
n-Pentanol (nPeOH)

Acetone (Ac)

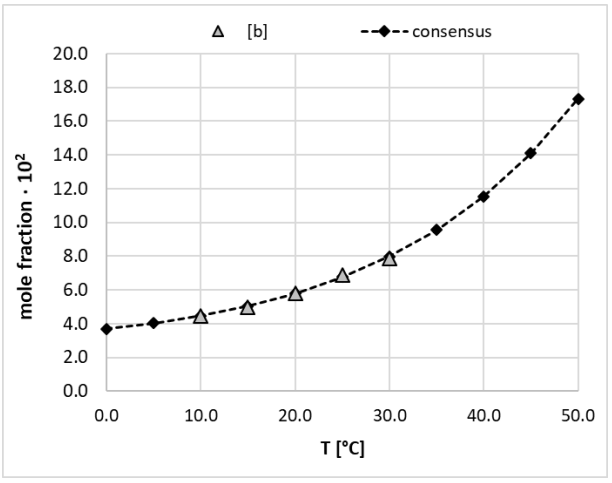




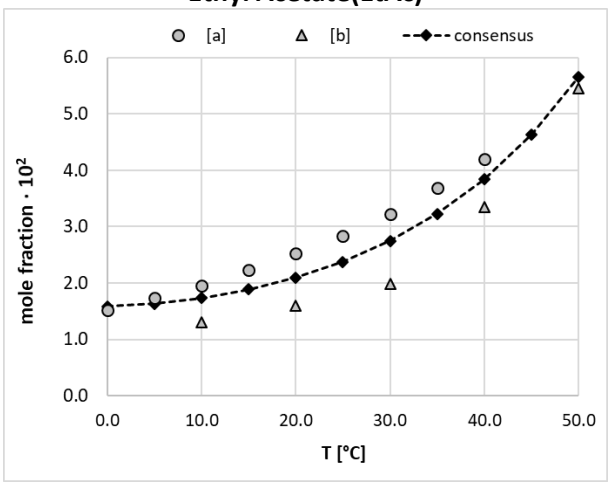
Acetonitrile



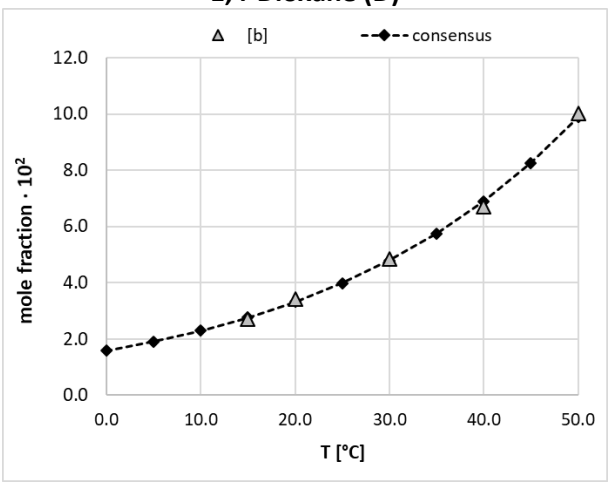
Dichloromethane



Ethyl Acetate(EtAc)



1,4-Dioxane (D)



Toluene (T)

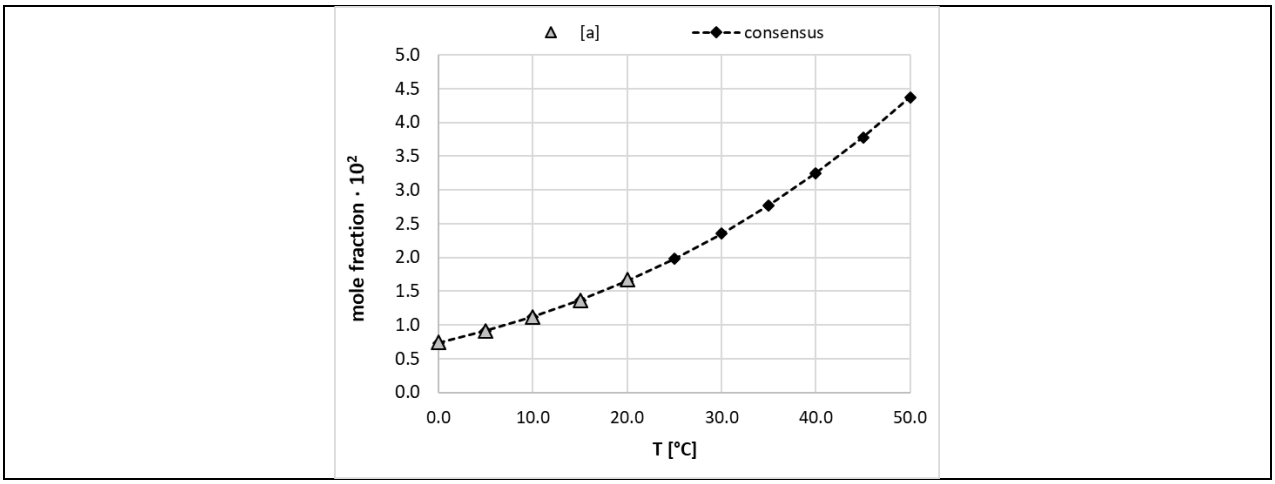


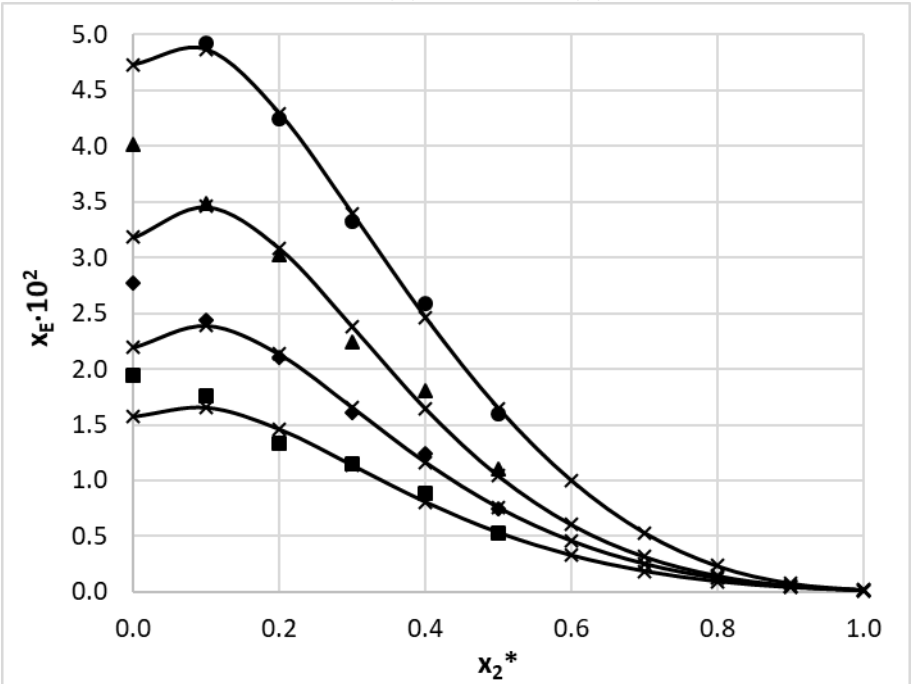
Figure S2.1. Graphical illustration of the solubility data curation of edaravone in neat solvents. The black diamonds represent curated values constituting the solubility dataset, while gray symbols characterize experimental points ([a], [b], [c] taken from references 18, 16, 17, respectively as cited in main text).

S2.2. Binary solvents mixtures

$$\ln x_{w,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1 w_2}{T/K} \sum_{i=0}^{2} J_i (w_1 - w_2)^i$$

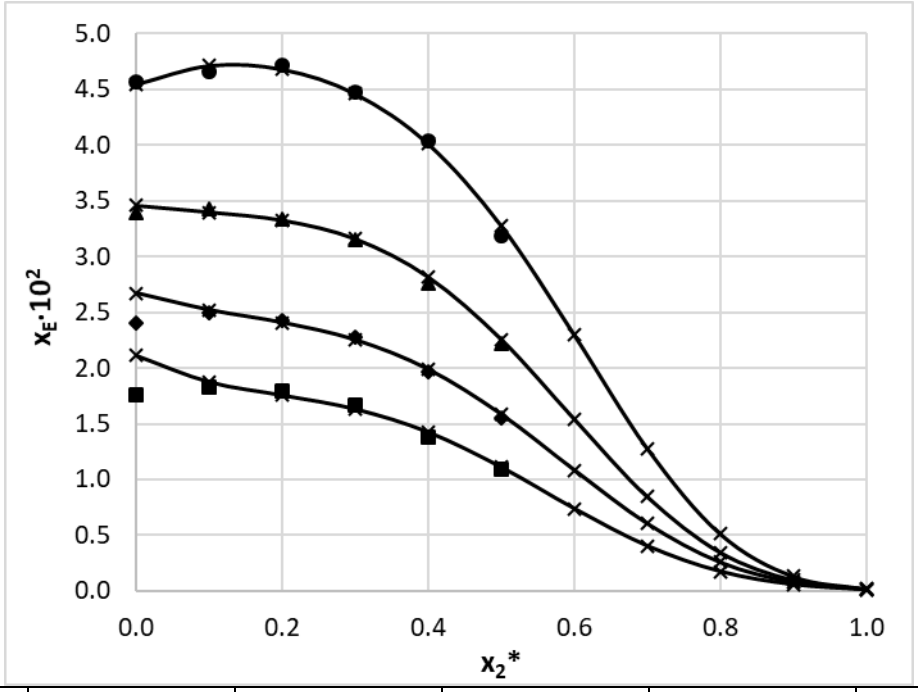
Table S2.2. Solubility data curation of edaravone in binary solvents. All experimental data come from reference 18 as cited in main text or from this work.

water (2) – methanol (3)



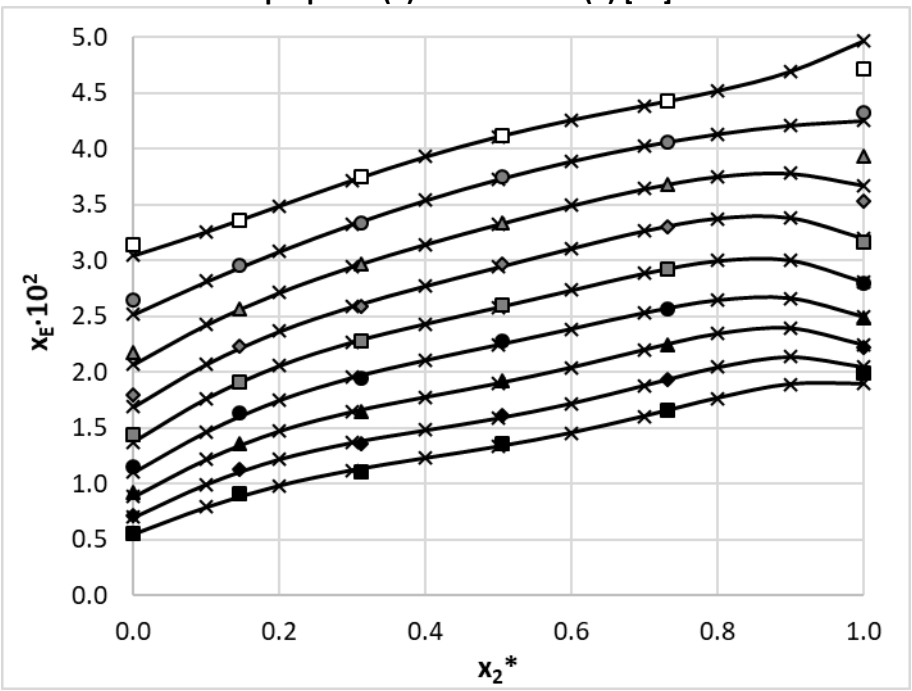
T[°C]	J_0	J_1	J_2	RMSD	MAPE
10.0	4.935	0.320	1.592	58.959	14.259
20.0	5.576	0.562	1.995	36.531	8.931
30.0	5.955	0.417	1.703	72.284	4.090
40.0	6.824	2.131	2.068	52.056	3.162
50.0	7.632	2.241	1.469	119.003	4.342

water (2)- ethanol (3) [18]



T[°C]	J_0	J_1	J_2	RMSD	MAPE
10.0	7.281	3.449	-0.574	32.544	6.264
20.0	8.122	4.338	0.587	30.913	5.251
30.0	8.877	4.757	0.964	49.154	5.418
40.0	9.646	5.615	2.082	58.181	5.770
50.0	10.520	6.562	3.602	87.403	6.526

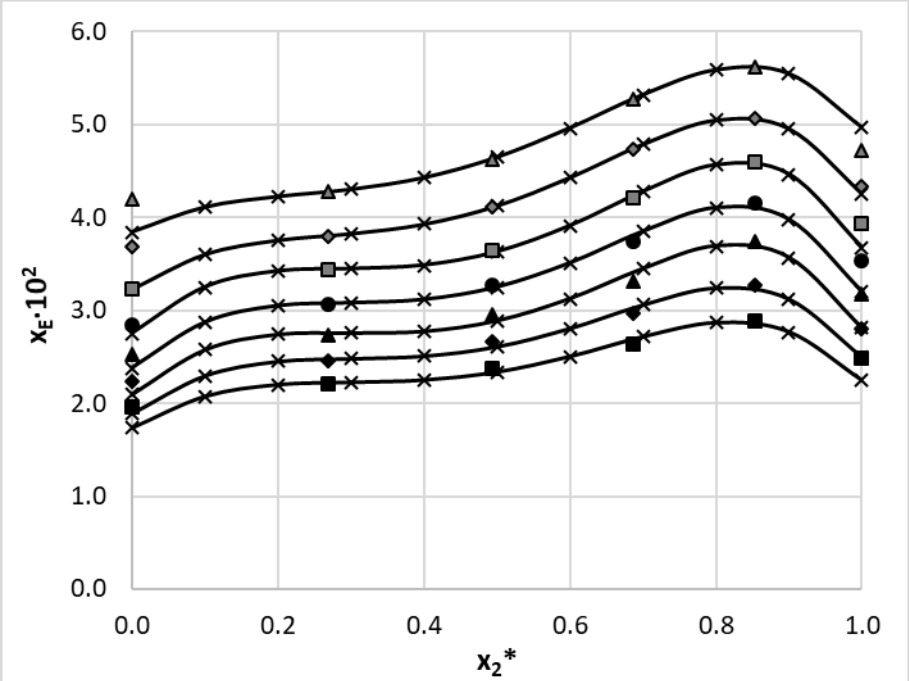
n-propanol (3) –acetonitrile (2) [18]



T[°C]	J_0	J_1	J_2	RMSD	MAPE
0.0	1.069	-0.816	1.467	15.902	1.065
5.0	1.131	-0.666	1.658	12.582	0.691

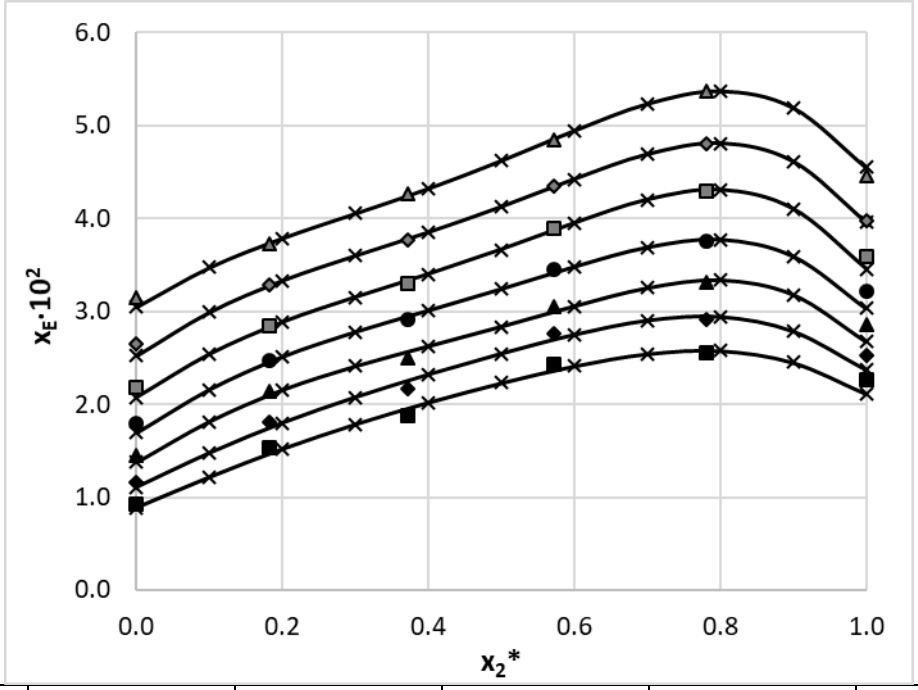
10.0	1.198	-0.494	1.470	13.761	0.629
15.0	1.204	-0.398	1.128	19.602	0.756
20.0	1.092	-0.275	1.030	6.988	0.228
25.0	0.936	-0.138	0.778	13.604	0.392
30.0	0.746	-0.106	0.453	3.783	0.096
35.0	0.521	-0.109	0.060	13.166	0.294
40.0	0.223	-0.180	-0.249	1.361	0.027

n-propanol (3) -ethyl acetate (2) [18]



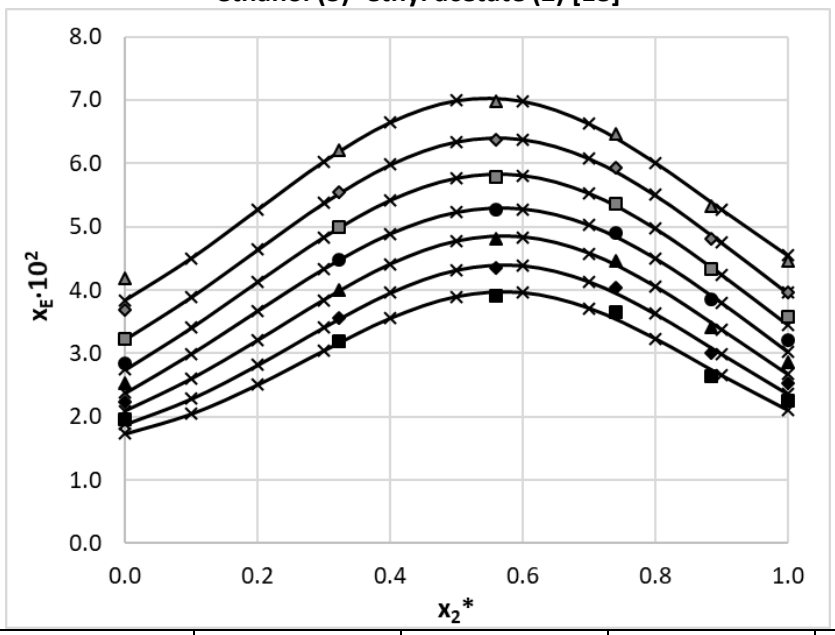
T[°C]	J_0	J_1	J_2	RMSD	MAPE
0.0	0.348	0.736	0.694	2.541	0.094
5.0	0.523	0.591	1.736	17.786	0.608
10.0	0.674	0.563	2.305	32.779	0.989
15.0	0.737	0.579	2.493	41.052	1.104
20.0	0.693	0.629	2.765	54.727	1.314
25.0	0.655	0.618	2.495	34.850	0.716
30.0	0.531	0.592	2.309	15.065	0.290
35.0	0.427	0.671	1.604	5.045	0.087
40.0	0.246	0.652	1.153	2.607	0.040

ethanol (3) –acetonitrile (2) [18]



T[°C]	J_0	J_1	J_2	RMSD	MAPE
0.0	2.244	-0.142	0.369	16.928	0.823
5.0	2.130	-0.042	0.741	27.080	1.264
10.0	1.959	0.039	0.986	49.030	1.951
15.0	1.810	0.182	1.075	50.854	1.740
20.0	1.570	0.198	1.470	39.716	1.175
25.0	1.433	0.297	1.346	25.193	0.621
30.0	1.255	0.491	1.274	18.085	0.407
35.0	1.066	0.501	1.135	4.698	0.093
40.0	0.865	0.566	0.927	10.274	0.180

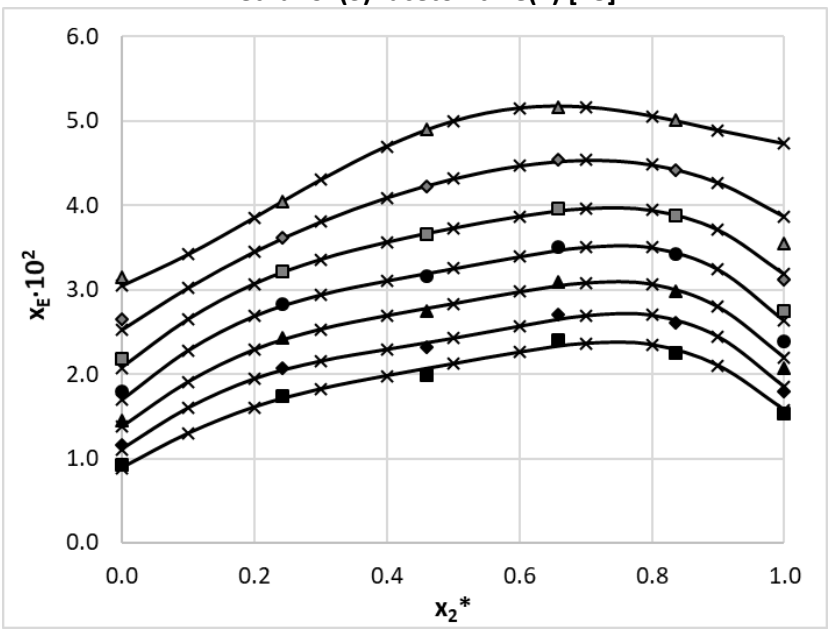
ethanol (3) -ethyl acetate (2) [18]



T[°C]	J_0	J_1	J_2	RMSD	MAPE
0.0	2.559	0.951	-1.637	102.143	2.974

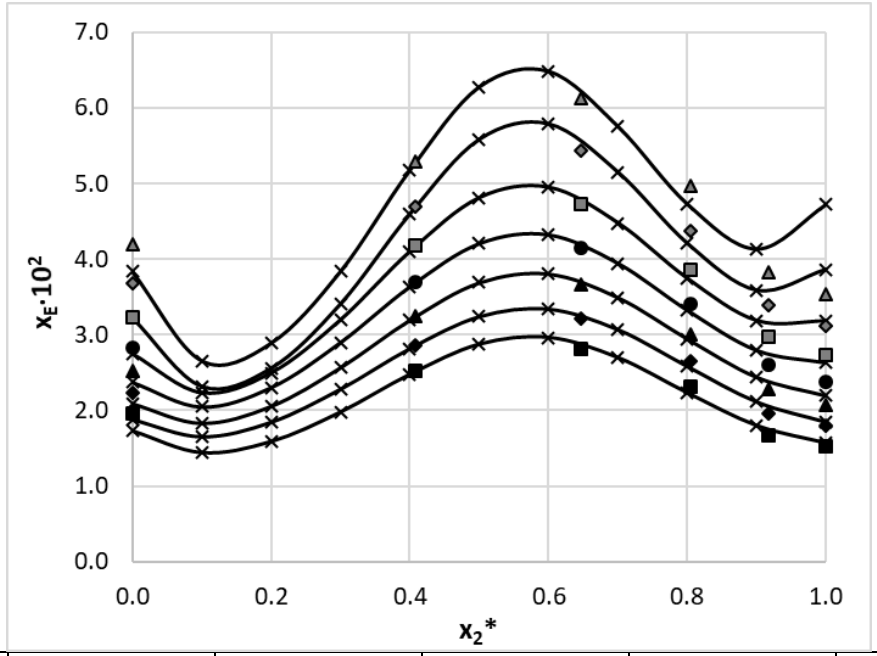
5.0	2.792	0.817	-1.586	91.718	2.223
10.0	2.843	0.714	-0.996	68.643	1.564
15.0	2.860	0.601	-0.737	55.115	1.117
20.0	2.805	0.463	-0.471	47.899	0.867
25.0	2.665	0.301	-0.192	35.629	0.579
30.0	2.503	0.246	-0.261	27.505	0.393
35.0	2.296	0.247	-0.361	37.908	0.502
40.0	2.058	0.159	-0.546	47.431	0.570

methanol (3) -acetonitrile(2) [18]



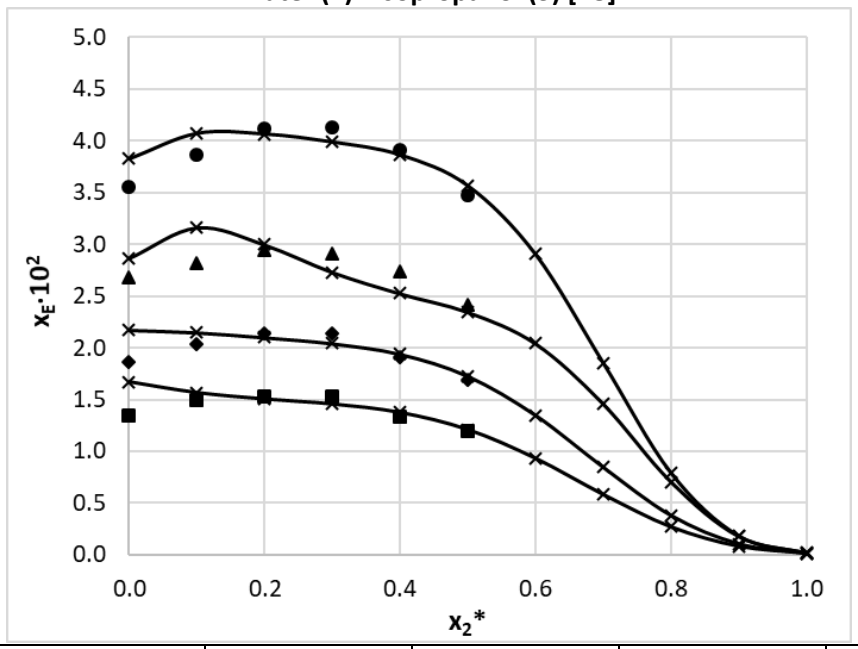
T[°C]	J_0	J_1	J_2	RMSD	MAPE
0.0	2.752	-0.076	1.068	24.958	1.287
5.0	2.534	0.047	1.954	40.614	1.634
10.0	2.350	0.179	2.151	49.757	1.839
15.0	2.113	0.109	2.314	36.525	1.162
20.0	1.960	0.051	1.891	26.510	0.726
25.0	1.726	-0.005	1.693	21.156	0.504
30.0	1.493	-0.034	1.118	12.033	0.242
35.0	1.293	0.030	0.405	9.733	0.178
40.0	1.098	0.043	-0.434	6.343	0.102

methanol (3) -ethyl acetate (2) [18]



T[°C]	J_0	J_1	J_2	RMSD	MAPE
0.0	1.765	1.825	-2.584	61.288	2.725
5.0	2.022	1.807	-2.824	52.796	2.027
10.0	2.220	2.071	-3.857	55.394	1.836
15.0	2.209	1.805	-3.397	55.023	1.589
20.0	2.172	1.724	-3.630	57.723	1.448
25.0	2.079	1.590	-4.015	71.032	1.563
30.0	1.948	1.661	-4.848	92.465	1.790
35.0	1.832	2.029	-6.378	117.226	2.005
40.0	1.551	1.919	-6.782	176.555	2.651

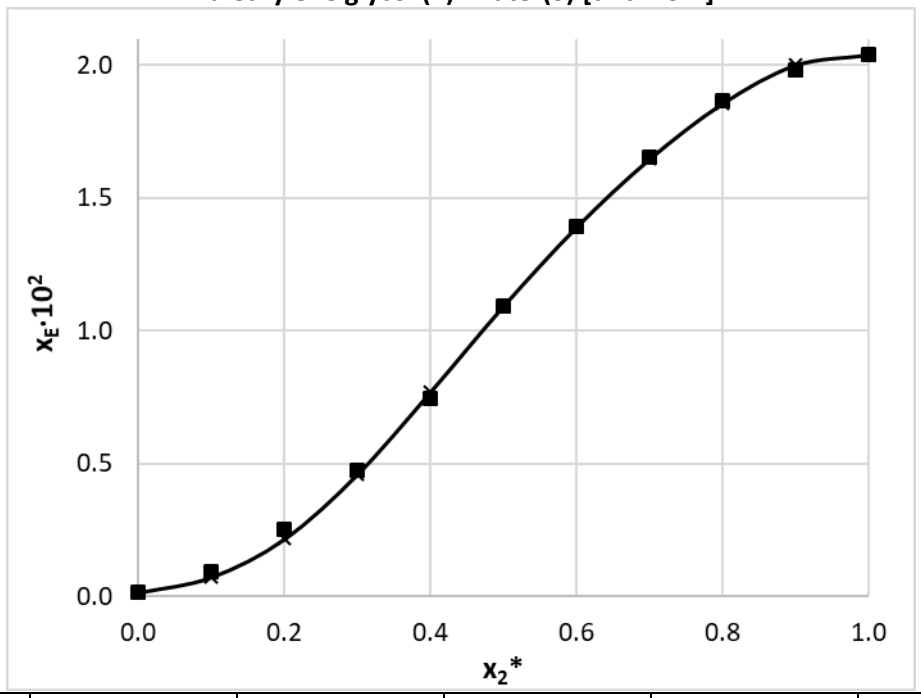
water (2) –Isopropanol (3) [18]



T[°C]	J_0	J_1	J_2	RMSD	MAPE
10.0	8.087	5.722	1.542	42.478	4.391

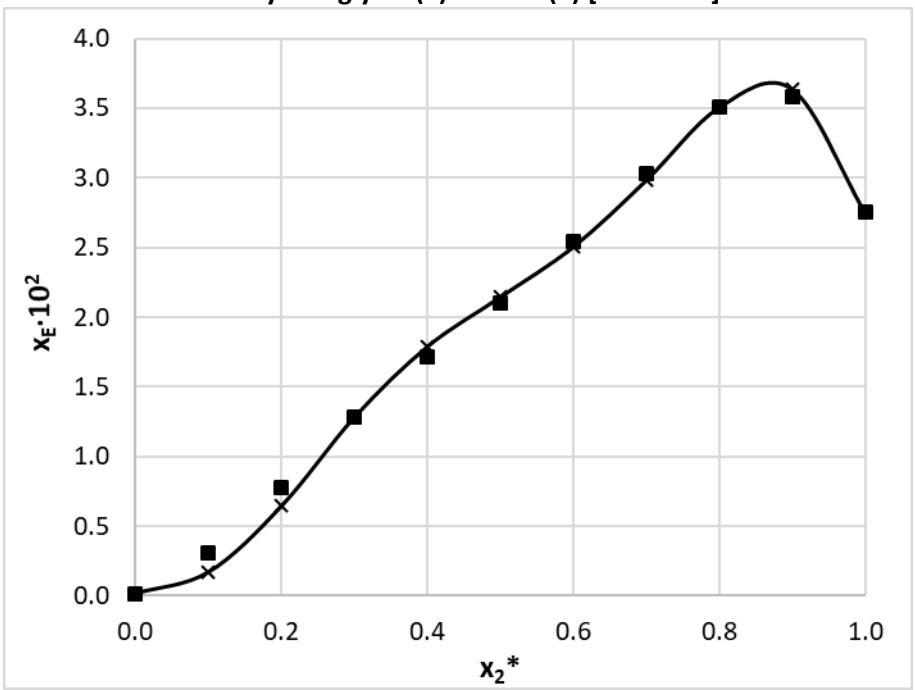
20.0	8.881	6.437	2.481	63.409	6.063
30.0	9.406	8.426	6.408	149.800	5.715
40.0	10.331	8.081	4.253	137.453	8.299
50.0	11.214	8.878	5.335	218.016	9.134

diethylene glycol (2) -water(3) [this work]



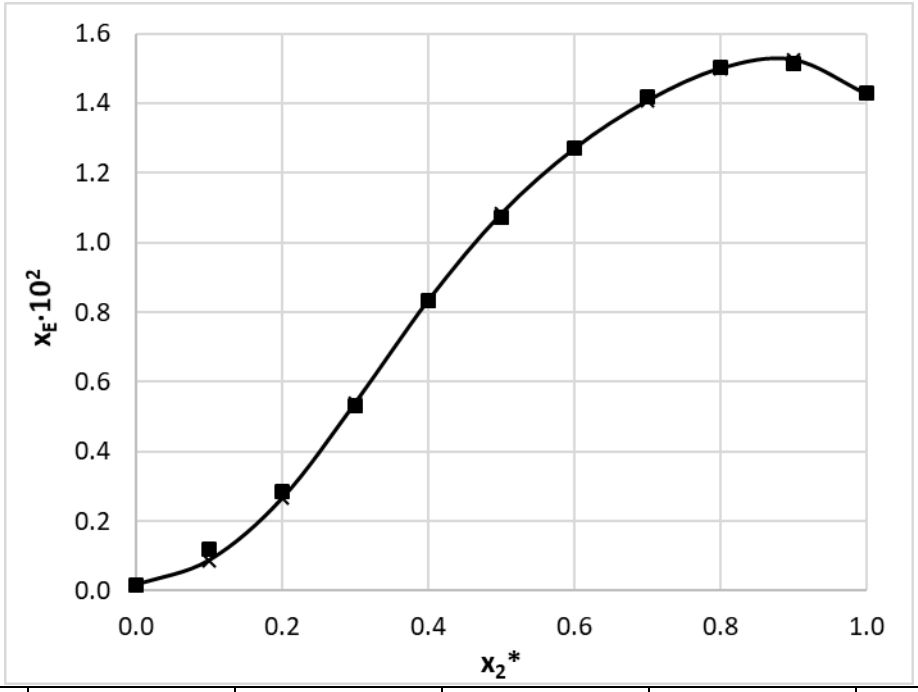
T[°C]	J_0	J_1	J_2	RMSD	MAPE
25.0	7.112	-3.865	1.720	16.725	3.815

triethylene glycol (2) –water (3) [this work]



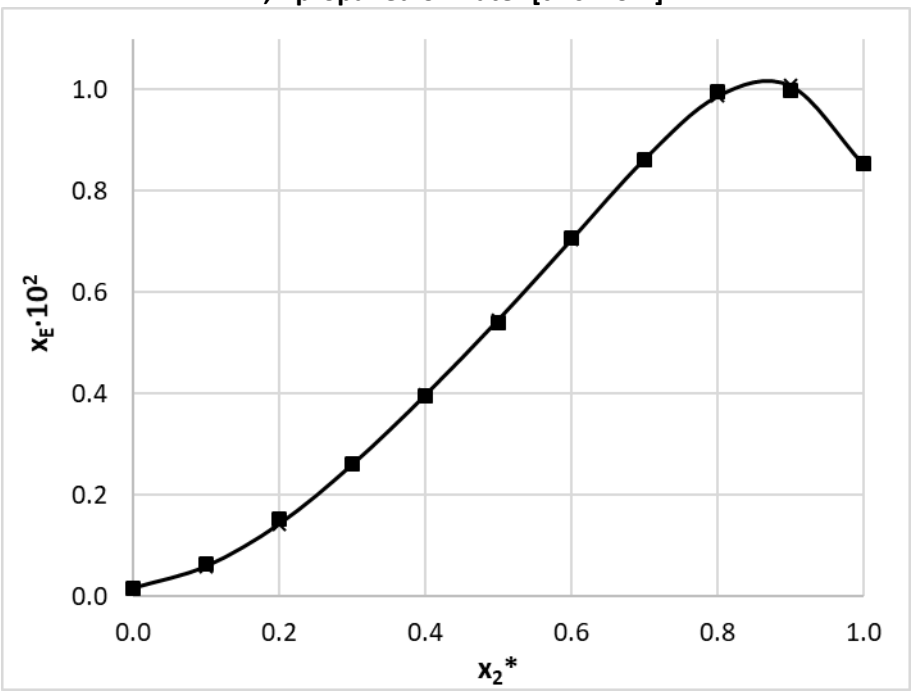
T[°C]	J_0	J_1	J_2	RMSD	MAPE
25.0	9.207	-7.124	8.221	67.058	6.571

1,3-butanediol-water-water [this work]



T[°C]	J_0	J_1	J_2	RMSD	MAPE
25.0	7.787	-4.889	2.818	13.222	3.480

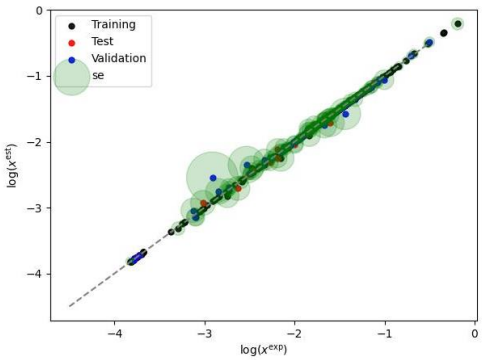
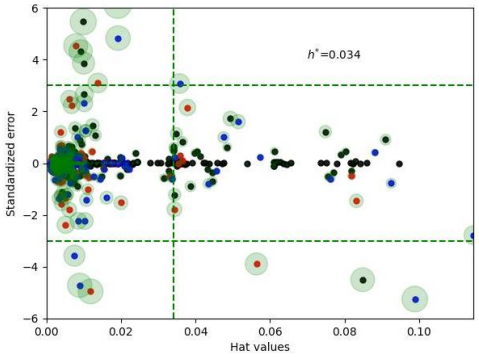
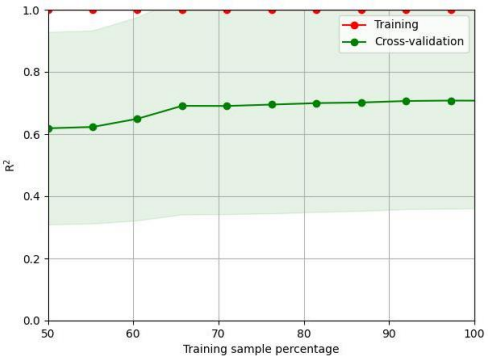
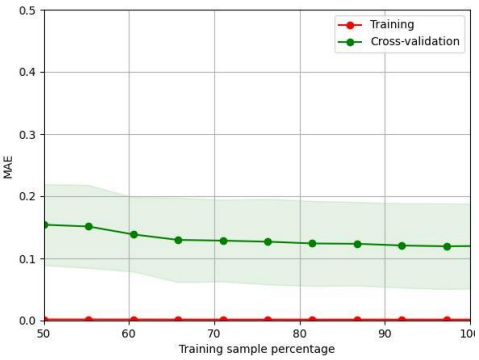
1,2-propanediol-water [this work]

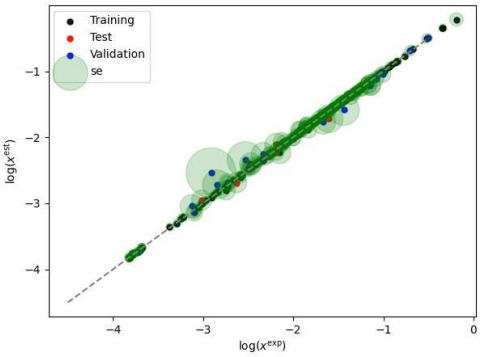
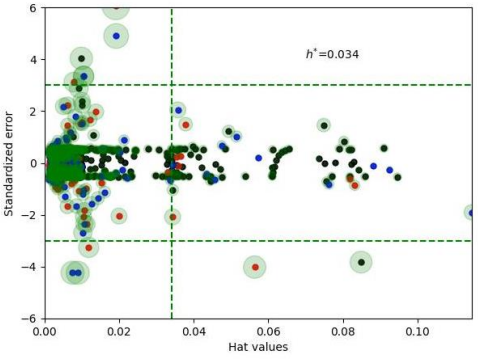


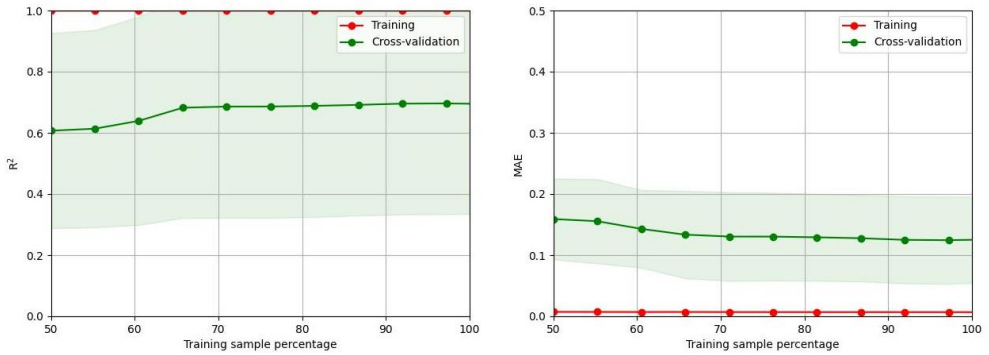
T[°C]	J_0	J_1	J_2	RMSD	MAPE
25.0	6.077	-2.239	3.021	5.422	1.480

S3. Regressor models characteristics

Table S3.1. Graphical illustration of the of the regression model performance belonging to set A. The panels a,b, and c document the correlation between computed and consensus solubility values with annotation of the standard deviation as circles radius, applicability domain plots, and results of learning curve analysis concerning both R2 and MAE, respectively.

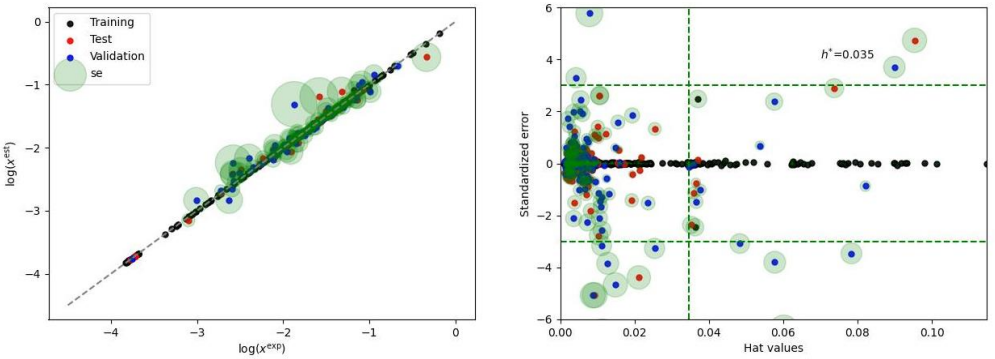
NuSVR	
a	b
	
c	
	

SVR	
a	b
	
c	

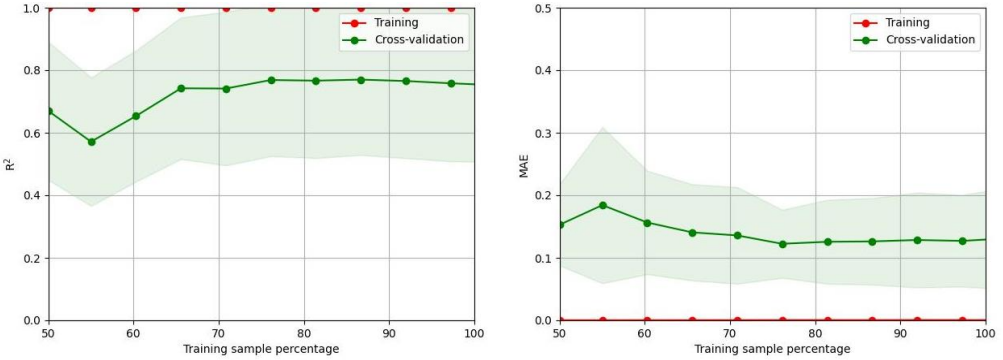


CatBoostRegressor

a b

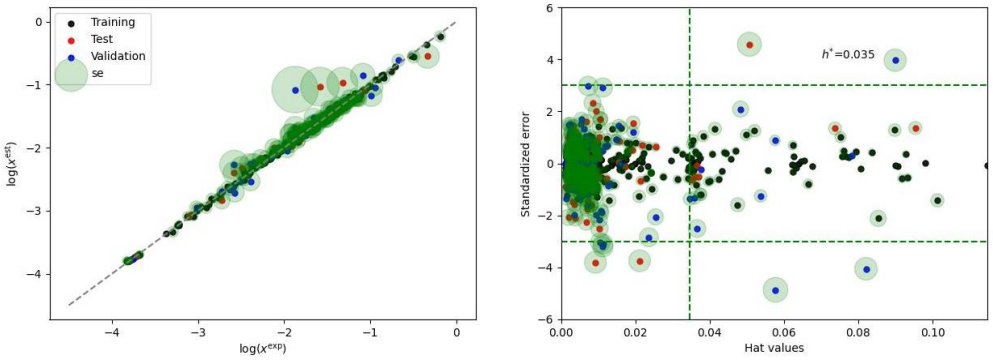


c

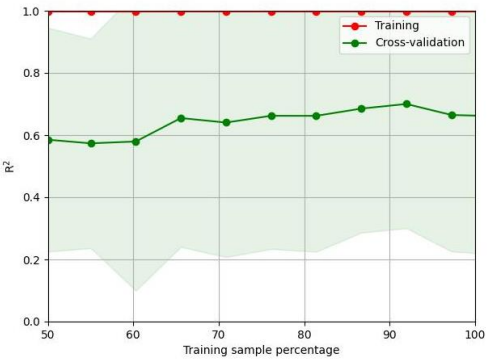


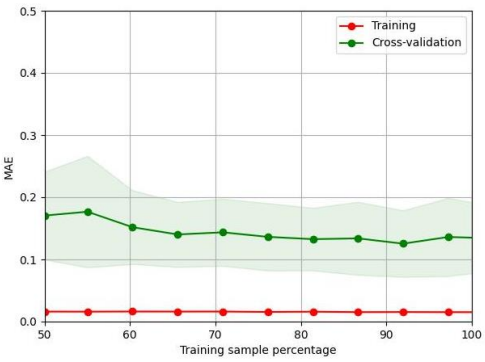
XGBRegressor

a b



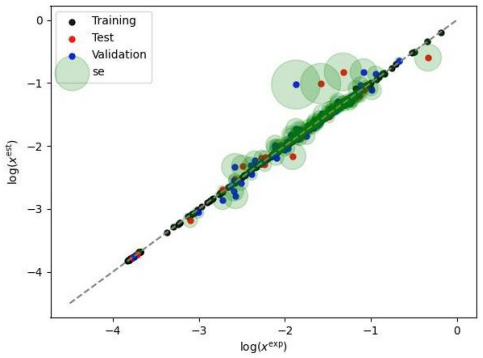
c



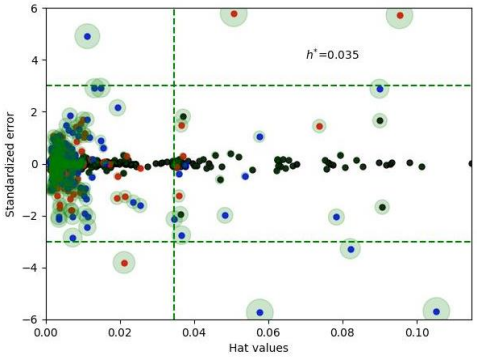


HistGradientBoostingRegressor

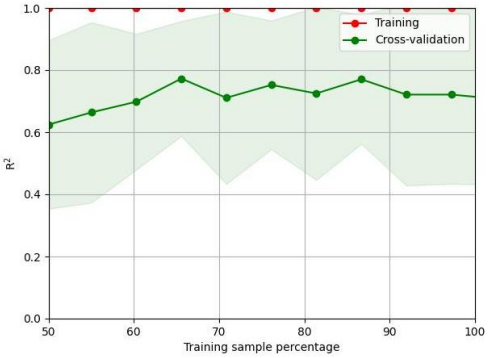
a



b



c



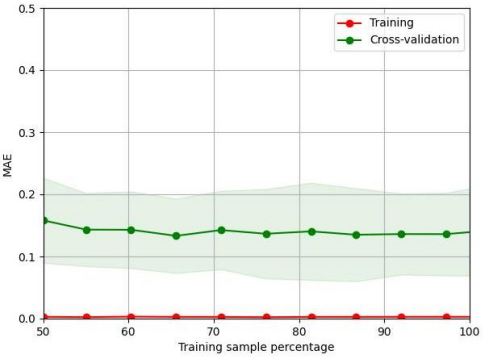
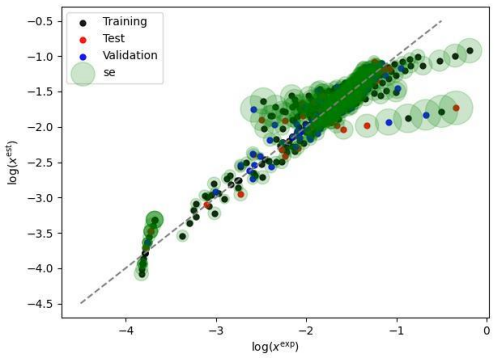
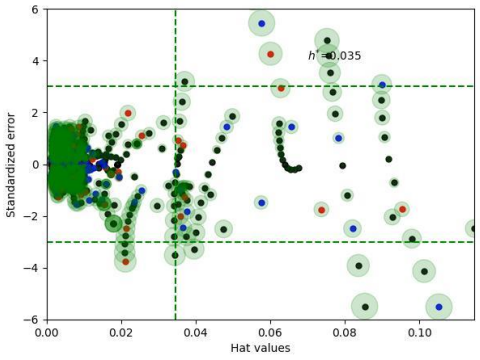
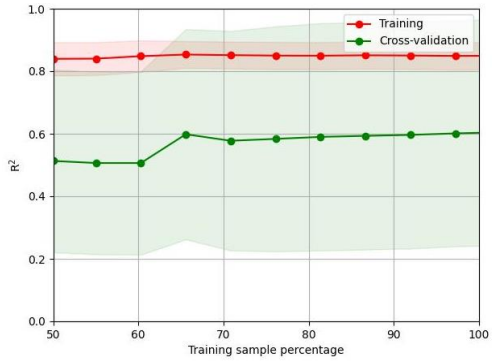
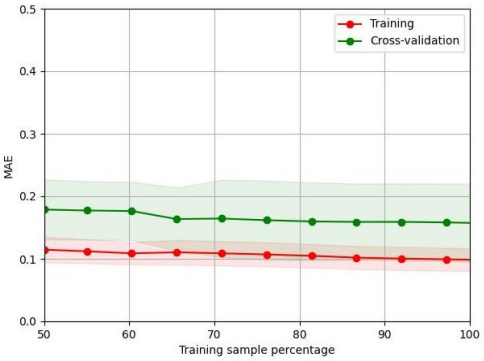
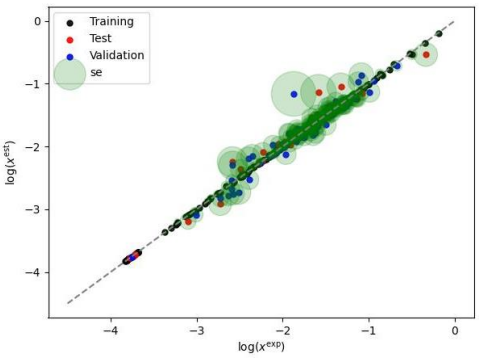
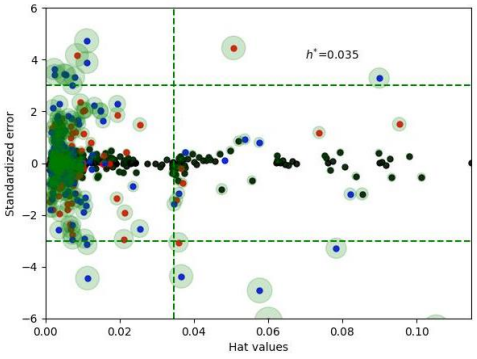
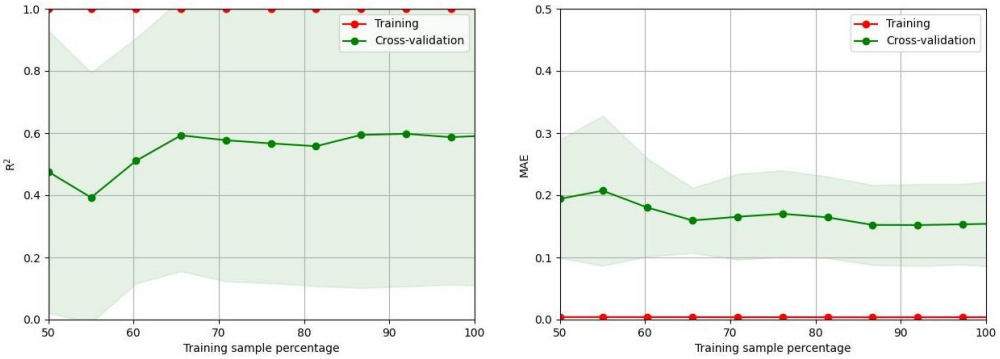


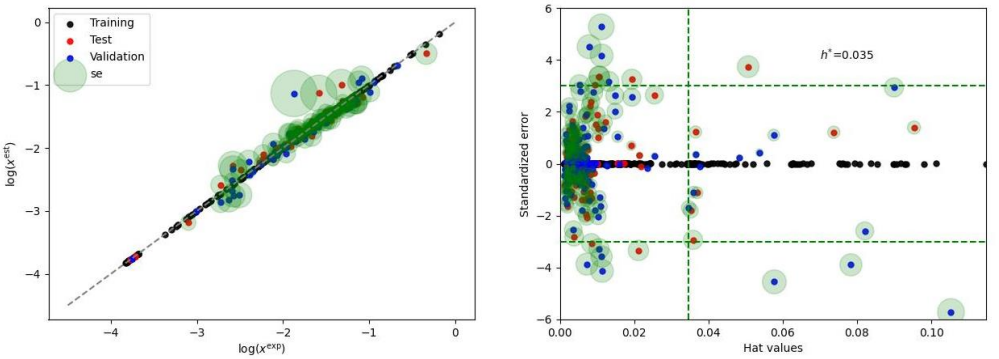
Table S3.2. Graphical illustration of the of the regression model performance belonging to set B. The panels a,b, and c document the correlation between computed and consensus solubility values with annotation of the standard deviation as circles radius, applicability domain plots, and results of learning curve analysis concerning both R2 and MAE, respectively.

GaussianProcessRegressor	
a	b
	
c	
	
BaggingRegressor	
a	b
	
c	

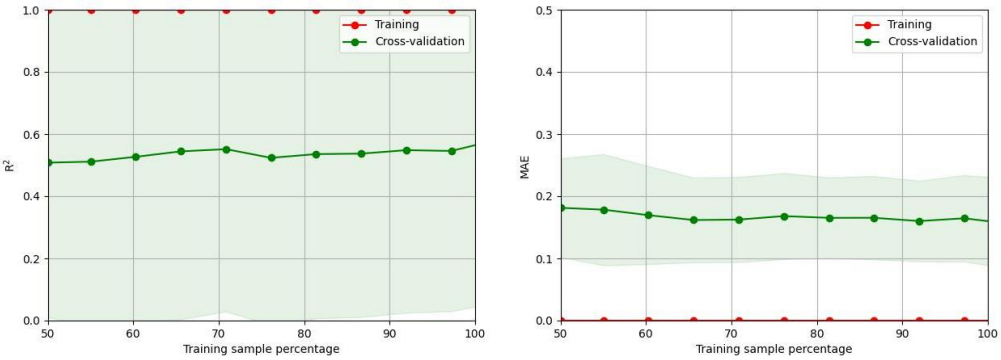


RandomForestRegressor

a b

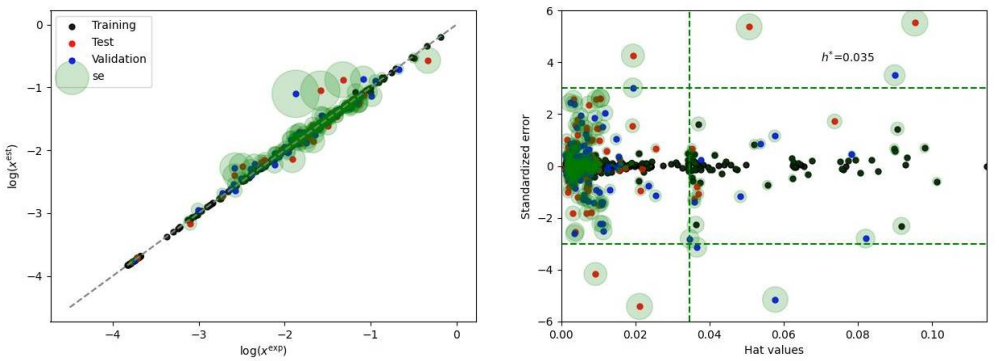


c



LGBMRegressor

a b



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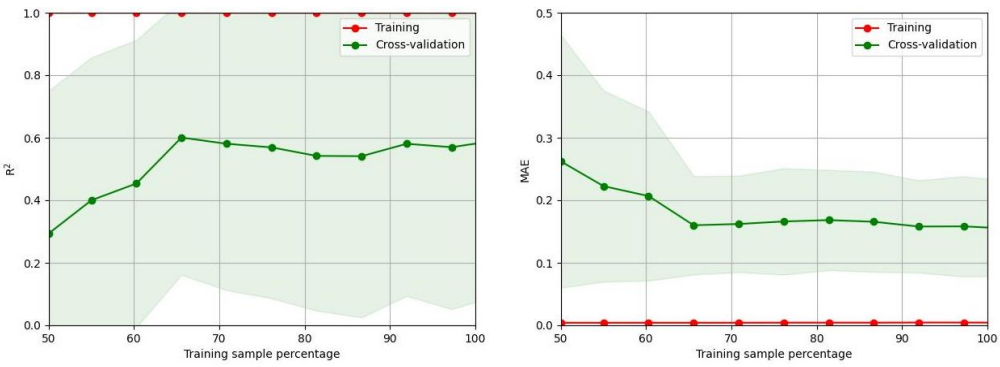
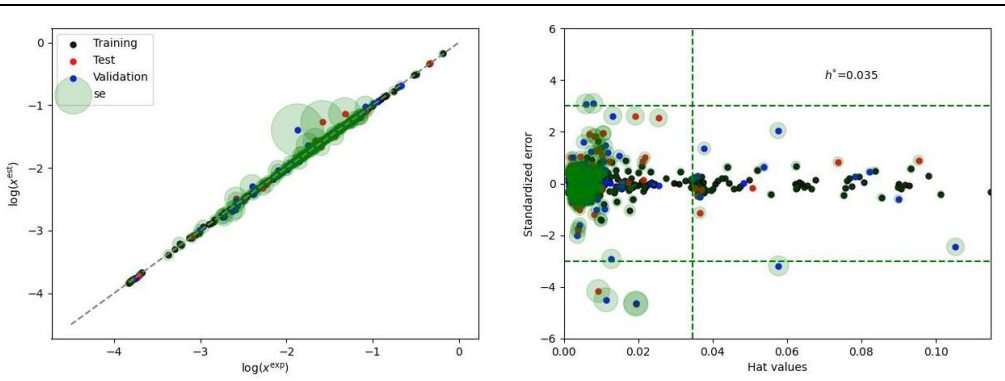


MLPRegressor

a b



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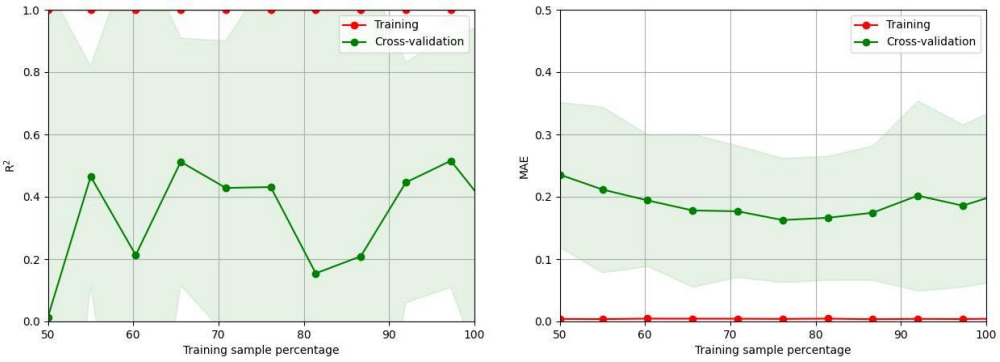
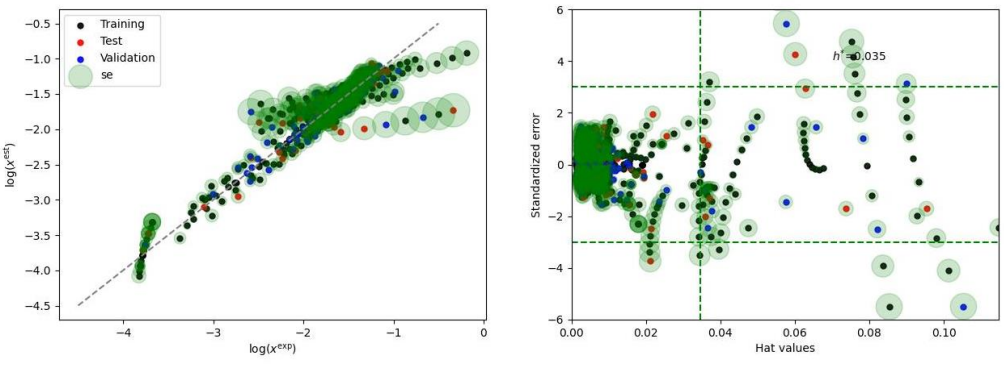
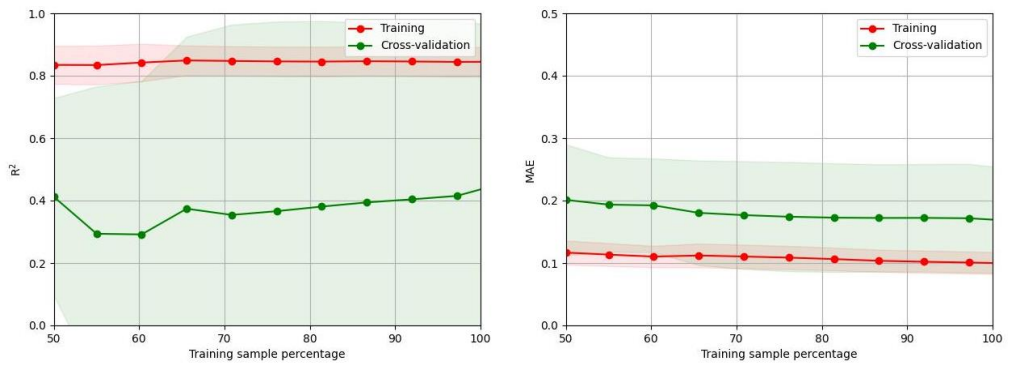


LassoLars

a b

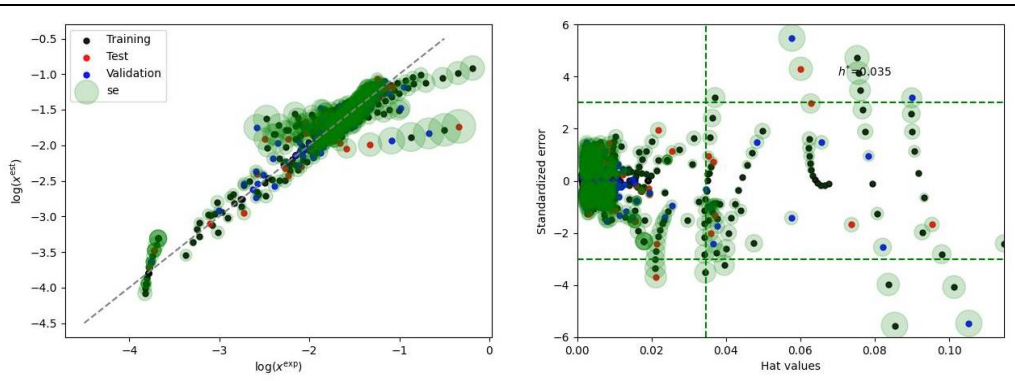


c

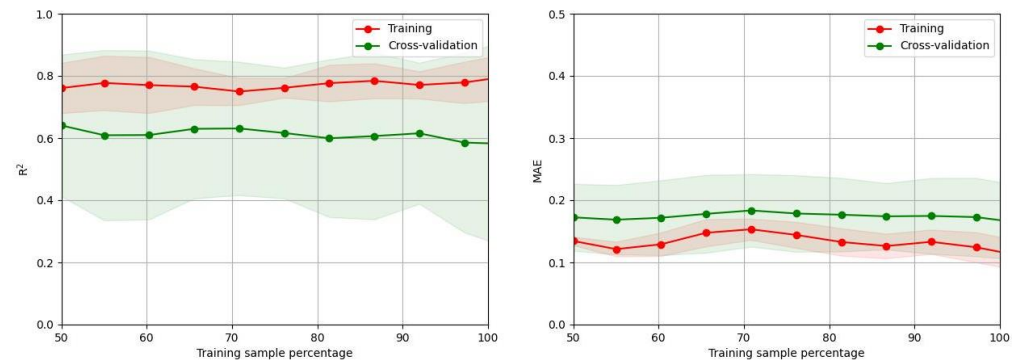


LassoLarsCV

a b

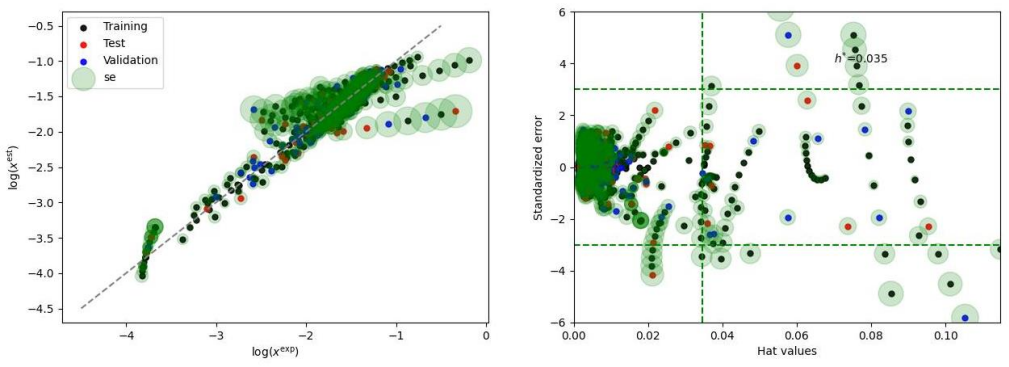


c



Ridge

a b



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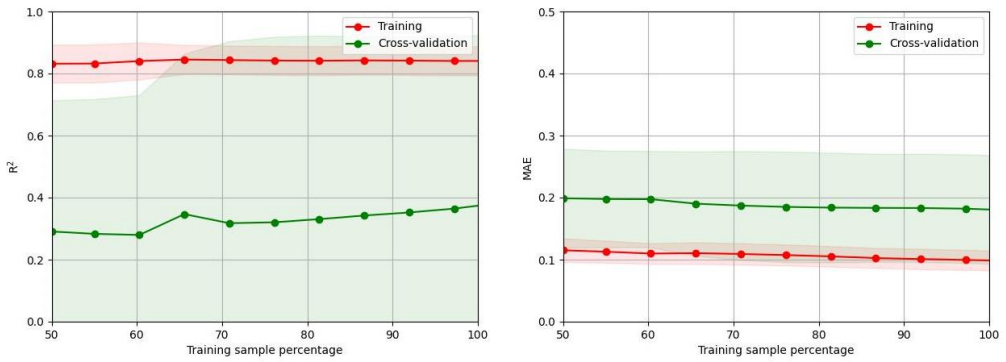
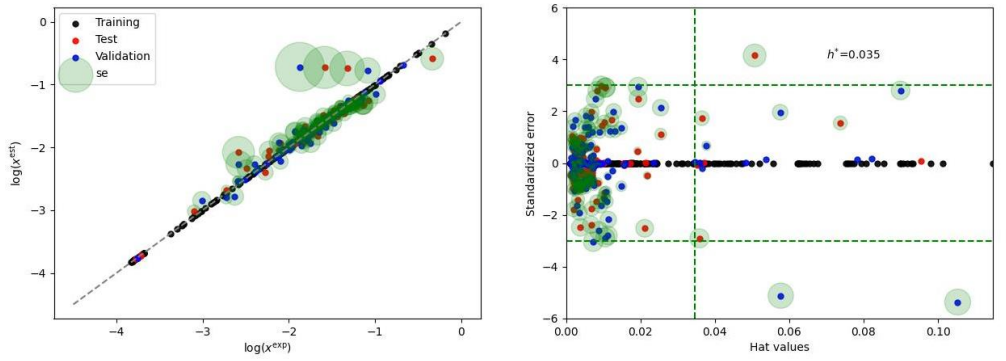


KNeighborsRegressor

a b



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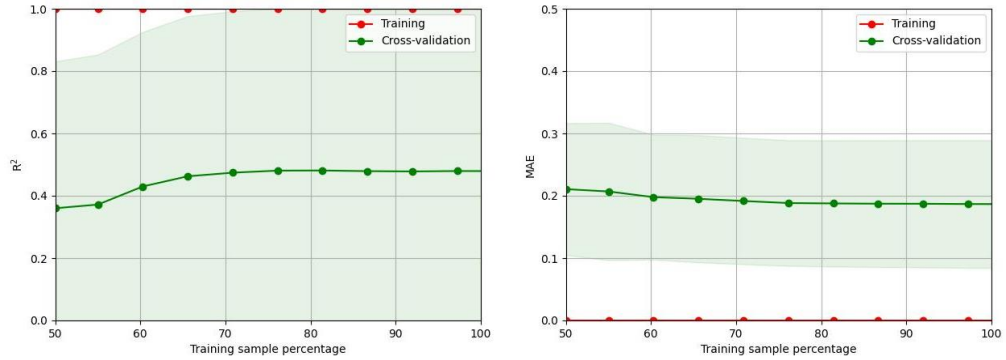
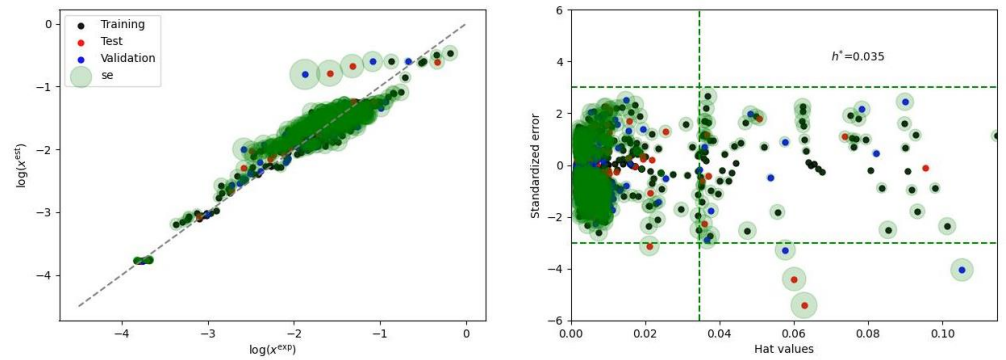


AdaBoostRegressor

a b



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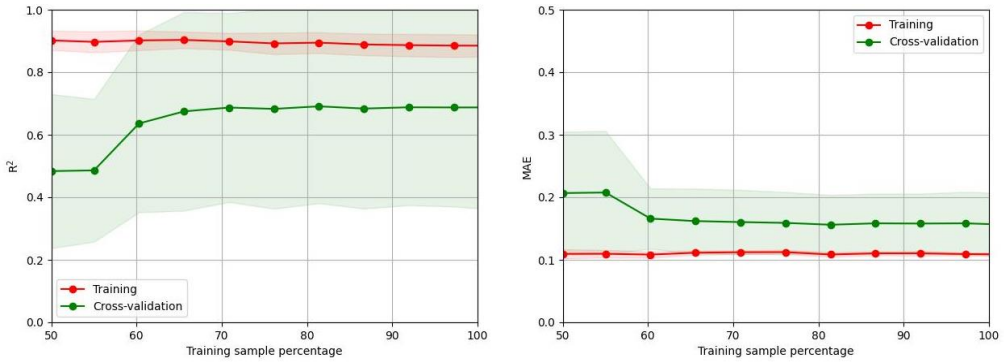
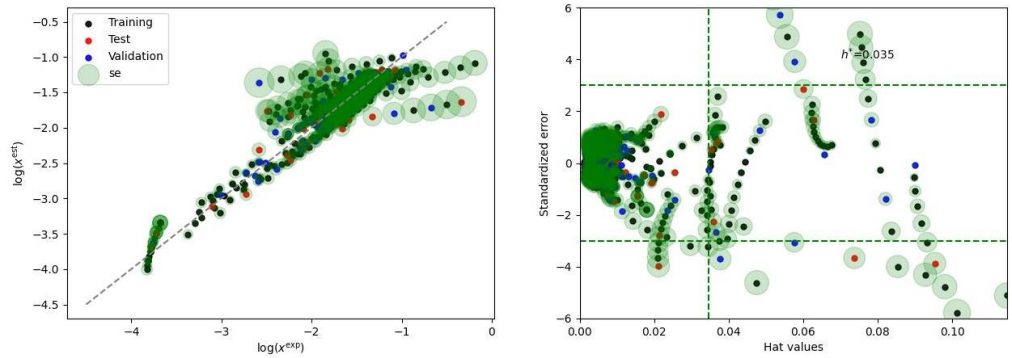


OrthogonalMatchingPursuitCV

a b



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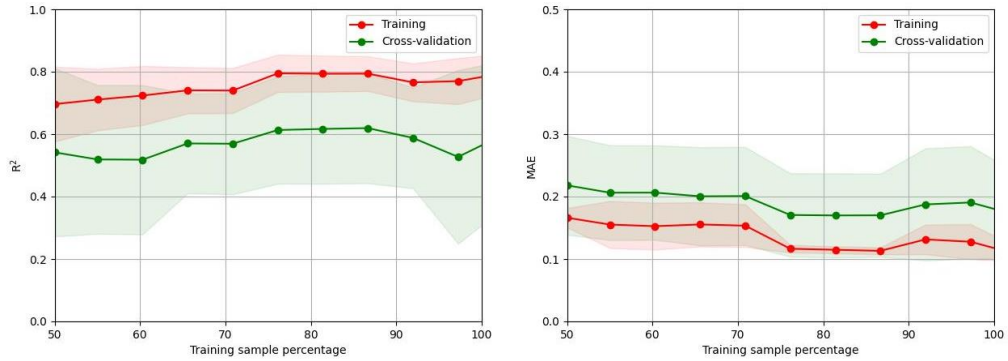
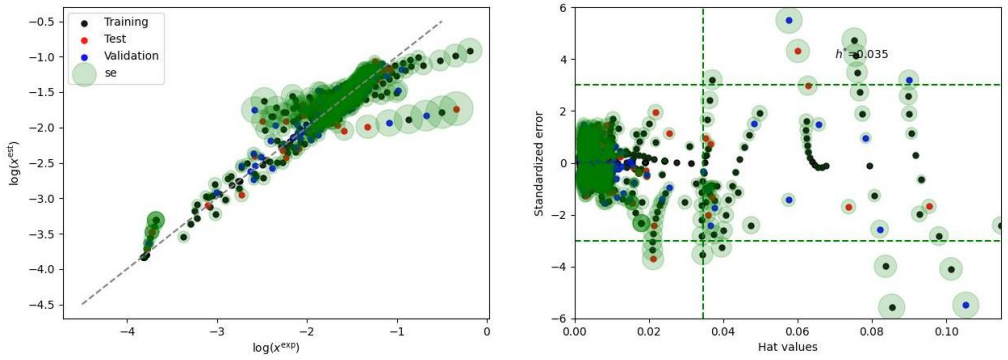


TransformedTargetRegressor

a b



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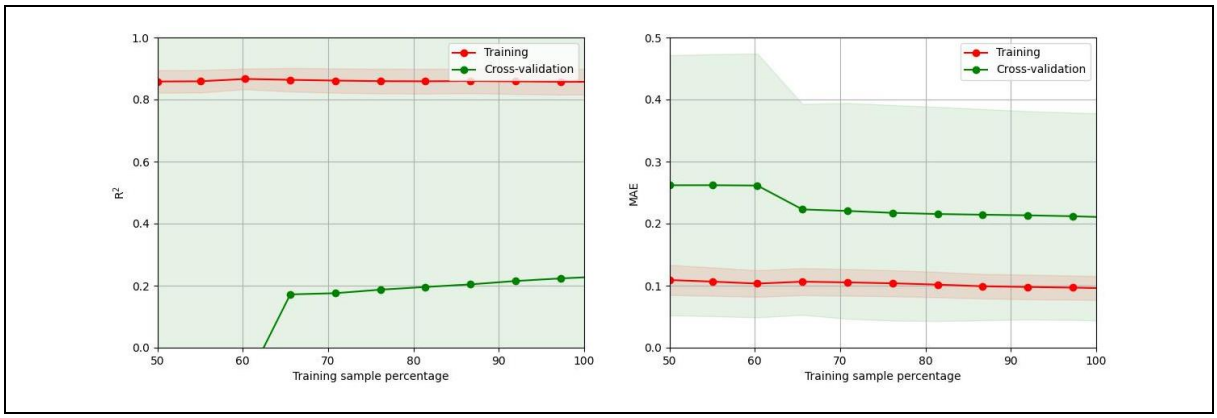
Training
Cross-validation
R^2
Training sample percentage
Training
Cross-validation
MAE
Training sample percentage