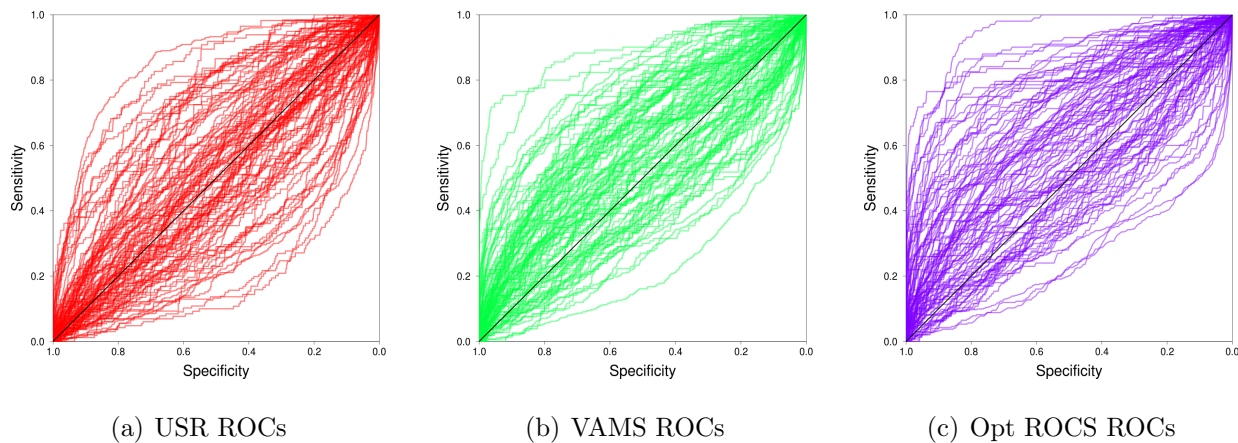


# SUPPLEMENTARY MATERIALS



**Figure S1:** The receiver operating characteristic curves for a selection of shape-based virtual screening algorithms. These curves plot the specificity (true negative rate) with respect to the sensitivity (true positive rate) as the threshold for classification is changed.

**Table S1:** Area under the curve (AUC) of ROC curves for various shape-based virtual screening algorithms.

Target					Color	Color	Color
	USR	VAMS	Unopt ROCS	Opt ROCS	USR	Unopt ROCS	Opt Rocs
aa2ar	0.507	0.562	0.569	0.601	0.533	0.606	0.705
abl1	0.348	0.434	0.509	0.552	0.338	0.514	0.614
ace	0.593	0.624	0.587	0.596	0.751	0.613	0.694
aces	0.265	0.226	0.212	0.261	0.278	0.242	0.517
ada	0.525	0.622	0.566	0.735	0.689	0.629	0.888
ada17	0.390	0.439	0.462	0.446	0.459	0.470	0.636
adrb1	0.385	0.469	0.438	0.378	0.397	0.426	0.465
adrb2	0.424	0.476	0.429	0.382	0.367	0.413	0.430
akt1	0.358	0.412	0.304	0.275	0.401	0.274	0.370
akt2	0.388	0.364	0.366	0.376	0.398	0.369	0.412
aldr	0.541	0.587	0.629	0.639	0.282	0.636	0.685
ampc	0.528	0.641	0.625	0.583	0.725	0.661	0.758
andr	0.535	0.589	0.533	0.569	0.685	0.570	0.691
aofb	0.315	0.418	0.436	0.397	0.364	0.440	0.379
bace1	0.480	0.436	0.306	0.320	0.483	0.315	0.313
braf	0.391	0.476	0.465	0.533	0.637	0.474	0.581
cah2	0.374	0.436	0.447	0.460	0.354	0.426	0.512
casp3	0.542	0.464	0.458	0.455	0.581	0.445	0.514

Target	USR	VAMS	Unopt ROCS	Opt ROCS	Color USR	Color Unopt ROCS	Color Opt Rocs
cdk2	0.567	0.673	0.701	0.724	0.694	0.715	0.703
comt	0.486	0.568	0.529	0.630	0.626	0.521	0.904
cp2c9	0.442	0.455	0.435	0.434	0.421	0.452	0.457
cp3a4	0.529	0.542	0.540	0.549	0.509	0.510	0.511
csflr	0.444	0.539	0.576	0.635	0.510	0.608	0.664
cxcr4	0.620	0.715	0.735	0.779	0.646	0.741	0.782
def	0.577	0.704	0.658	0.748	0.774	0.654	0.860
dhi1	0.518	0.655	0.628	0.680	0.464	0.623	0.617
dpp4	0.647	0.633	0.643	0.655	0.643	0.647	0.681
drd3	0.281	0.333	0.324	0.299	0.189	0.315	0.312
dyr	0.389	0.390	0.404	0.444	0.643	0.473	0.735
egfr	0.489	0.549	0.578	0.662	0.532	0.625	0.769
esr1	0.475	0.579	0.596	0.648	0.686	0.619	0.734
esr2	0.475	0.582	0.587	0.648	0.815	0.678	0.783
fa10	0.650	0.640	0.636	0.656	0.601	0.641	0.712
fa7	0.620	0.536	0.602	0.522	0.857	0.599	0.614
fabp4	0.740	0.752	0.752	0.801	0.379	0.744	0.788
fak1	0.490	0.645	0.749	0.865	0.690	0.771	0.949
fgfr1	0.228	0.368	0.402	0.438	0.293	0.421	0.557
fbk1a	0.547	0.662	0.585	0.638	0.377	0.561	0.622
fnta	0.552	0.619	0.547	0.659	0.599	0.557	0.777
fpps	0.785	0.850	0.820	0.872	0.631	0.825	0.986
gcr	0.500	0.494	0.419	0.490	0.627	0.446	0.592
glcm	0.400	0.388	0.424	0.439	0.492	0.428	0.519
gria2	0.450	0.472	0.543	0.622	0.509	0.562	0.681
grik1	0.452	0.573	0.656	0.633	0.488	0.665	0.726
hdac2	0.278	0.451	0.430	0.416	0.182	0.403	0.436
hdac8	0.538	0.418	0.380	0.505	0.769	0.415	0.653
hivint	0.452	0.425	0.409	0.456	0.299	0.408	0.474
hivpr	0.742	0.778	0.747	0.724	0.733	0.772	0.693
hivrt	0.616	0.688	0.697	0.634	0.665	0.688	0.609
hmdh	0.601	0.771	0.775	0.841	0.570	0.775	0.909
hs90a	0.727	0.664	0.624	0.714	0.692	0.633	0.734
hvk4	0.505	0.395	0.470	0.632	0.719	0.491	0.808
igf1r	0.338	0.341	0.349	0.486	0.518	0.353	0.547
inha	0.345	0.492	0.505	0.638	0.516	0.524	0.718
ital	0.578	0.483	0.450	0.532	0.473	0.470	0.477
jak2	0.471	0.673	0.696	0.785	0.664	0.711	0.809
kif11	0.610	0.678	0.671	0.763	0.693	0.714	0.759
kit	0.192	0.368	0.377	0.408	0.278	0.387	0.481
kith	0.704	0.618	0.573	0.478	0.751	0.558	0.681
kpcb	0.691	0.660	0.684	0.751	0.715	0.703	0.801
lck	0.246	0.296	0.406	0.432	0.246	0.416	0.446

Target					Color	Color	Color
	USR	VAMS	Unopt ROCS	Opt ROCS	USR	Unopt ROCS	Opt Rocs
lkha4	0.518	0.610	0.621	0.661	0.478	0.623	0.787
mapk2	0.429	0.732	0.715	0.736	0.533	0.724	0.856
mcr	0.562	0.574	0.490	0.546	0.788	0.575	0.663
met	0.747	0.748	0.777	0.765	0.765	0.790	0.812
mk01	0.423	0.486	0.561	0.531	0.489	0.599	0.729
mk10	0.458	0.527	0.514	0.486	0.531	0.529	0.556
mk14	0.586	0.559	0.556	0.590	0.605	0.555	0.568
mmp13	0.513	0.532	0.493	0.554	0.670	0.492	0.687
mp2k1	0.512	0.528	0.569	0.486	0.434	0.575	0.526
nos1	0.321	0.436	0.412	0.380	0.361	0.394	0.378
nram	0.815	0.810	0.755	0.800	0.493	0.751	0.865
pa2ga	0.539	0.612	0.598	0.645	0.549	0.609	0.711
parp1	0.585	0.717	0.704	0.656	0.637	0.709	0.712
pde5a	0.466	0.588	0.528	0.611	0.562	0.538	0.615
pgh1	0.468	0.693	0.731	0.727	0.604	0.715	0.635
pgh2	0.564	0.738	0.739	0.806	0.660	0.735	0.750
plk1	0.423	0.494	0.516	0.549	0.535	0.536	0.557
pnph	0.690	0.629	0.656	0.810	0.729	0.678	0.918
ppara	0.856	0.774	0.806	0.818	0.795	0.798	0.800
ppard	0.575	0.546	0.581	0.617	0.373	0.597	0.686
pparg	0.665	0.566	0.626	0.623	0.298	0.648	0.732
prgr	0.628	0.679	0.678	0.692	0.604	0.679	0.704
ptn1	0.223	0.322	0.318	0.327	0.113	0.303	0.290
pur2	0.649	0.564	0.565	0.489	0.756	0.614	0.898
pygm	0.454	0.471	0.504	0.478	0.576	0.535	0.461
pyrd	0.779	0.867	0.882	0.899	0.466	0.853	0.856
reni	0.729	0.677	0.601	0.603	0.587	0.599	0.573
rock1	0.505	0.447	0.423	0.470	0.525	0.456	0.609
rxra	0.464	0.509	0.438	0.668	0.349	0.563	0.900
sahh	0.742	0.534	0.557	0.874	0.912	0.713	0.995
src	0.560	0.590	0.600	0.666	0.518	0.600	0.585
tgfr1	0.506	0.644	0.632	0.680	0.520	0.639	0.721
thb	0.698	0.706	0.762	0.818	0.671	0.772	0.887
thrb	0.641	0.448	0.400	0.418	0.573	0.420	0.516
try1	0.726	0.656	0.588	0.531	0.723	0.596	0.574
tryb1	0.311	0.373	0.421	0.399	0.352	0.454	0.481
tysy	0.708	0.636	0.637	0.679	0.790	0.669	0.730
urok	0.328	0.412	0.375	0.412	0.439	0.382	0.499
vgfr2	0.694	0.637	0.673	0.715	0.597	0.682	0.687
wee1	0.453	0.573	0.632	0.941	0.804	0.690	0.981
xiap	0.675	0.652	0.537	0.727	0.848	0.606	0.923
Average	0.520	0.560	0.557	0.596	0.554	0.572	0.663

**Table S2:** BEDROC measures of early retrieval for various shape-based virtual screening algorithms. Calculations were performed using the CROC python package<sup>43</sup>.

Target					Color	Color	Color
	USR	VAMS	Unopt ROCS	Opt ROCS	USR	Unopt ROCS	Opt Rocs
aa2ar	0.095	0.114	0.126	0.175	0.039	0.161	0.293
abl1	0.048	0.092	0.113	0.158	0.085	0.146	0.249
ace	0.073	0.137	0.109	0.097	0.326	0.151	0.256
aces	0.012	0.012	0.017	0.052	0.023	0.026	0.093
ada	0.084	0.102	0.142	0.204	0.320	0.203	0.675
ada17	0.069	0.093	0.073	0.072	0.097	0.094	0.226
adrb1	0.050	0.110	0.117	0.106	0.073	0.115	0.184
adrb2	0.063	0.105	0.099	0.096	0.059	0.109	0.133
akt1	0.031	0.032	0.029	0.026	0.051	0.033	0.069
akt2	0.076	0.065	0.091	0.112	0.156	0.090	0.149
aldr	0.077	0.205	0.268	0.245	0.000	0.310	0.453
ampc	0.055	0.265	0.189	0.303	0.422	0.221	0.471
andr	0.089	0.151	0.123	0.164	0.288	0.174	0.319
aofb	0.045	0.065	0.072	0.067	0.061	0.056	0.054
bace1	0.033	0.016	0.016	0.022	0.021	0.015	0.043
braf	0.093	0.181	0.172	0.288	0.202	0.186	0.342
cah2	0.035	0.052	0.064	0.057	0.037	0.052	0.142
casp3	0.068	0.060	0.061	0.045	0.226	0.062	0.082
cdk2	0.108	0.189	0.219	0.255	0.250	0.225	0.270
comt	0.089	0.146	0.112	0.257	0.299	0.182	0.738
cp2c9	0.041	0.089	0.068	0.093	0.059	0.066	0.077
cp3a4	0.076	0.095	0.086	0.126	0.066	0.064	0.053
csflr	0.155	0.303	0.285	0.324	0.111	0.298	0.336
cxcr4	0.029	0.168	0.204	0.457	0.099	0.294	0.490
def	0.114	0.240	0.242	0.393	0.351	0.279	0.557
dhi1	0.069	0.202	0.177	0.265	0.066	0.183	0.269
dpp4	0.132	0.163	0.190	0.172	0.228	0.234	0.259
drd3	0.025	0.042	0.051	0.038	0.010	0.040	0.035
dyr	0.045	0.064	0.054	0.082	0.387	0.193	0.474
egfr	0.056	0.138	0.175	0.184	0.083	0.218	0.391
esr1	0.092	0.259	0.312	0.353	0.333	0.352	0.544
esr2	0.095	0.167	0.168	0.312	0.428	0.256	0.481
fa10	0.107	0.144	0.141	0.181	0.137	0.161	0.323
fa7	0.112	0.047	0.077	0.108	0.458	0.087	0.232
fabp4	0.367	0.209	0.320	0.467	0.000	0.340	0.432
fak1	0.052	0.187	0.290	0.476	0.143	0.313	0.864
fgfr1	0.036	0.057	0.046	0.035	0.009	0.057	0.061
fkbl1a	0.063	0.106	0.087	0.124	0.015	0.075	0.094
fnta	0.117	0.100	0.063	0.132	0.140	0.079	0.337
fpps	0.314	0.682	0.657	0.707	0.178	0.698	0.923

Target	USR	VAMS	Unopt ROCS	Opt ROCS	Color USR	Color Unopt ROCS	Color Opt Rocs
gcr	0.090	0.127	0.092	0.161	0.142	0.097	0.171
glcm	0.051	0.063	0.098	0.086	0.140	0.117	0.173
gria2	0.134	0.094	0.186	0.364	0.152	0.179	0.409
grik1	0.059	0.101	0.158	0.148	0.036	0.163	0.245
hdac2	0.035	0.110	0.111	0.081	0.038	0.092	0.100
hdac8	0.058	0.070	0.058	0.123	0.482	0.079	0.321
hivint	0.028	0.050	0.062	0.107	0.000	0.046	0.072
hivpr	0.317	0.274	0.257	0.210	0.173	0.300	0.175
hivrt	0.139	0.147	0.176	0.111	0.160	0.164	0.146
hmdh	0.255	0.380	0.380	0.560	0.271	0.391	0.730
hs90a	0.118	0.206	0.173	0.266	0.165	0.191	0.453
hvk4	0.102	0.248	0.272	0.398	0.417	0.290	0.523
igflr	0.042	0.040	0.063	0.135	0.141	0.089	0.196
inha	0.026	0.116	0.124	0.253	0.155	0.156	0.340
ital	0.077	0.177	0.160	0.175	0.007	0.158	0.166
jak2	0.039	0.217	0.216	0.345	0.098	0.237	0.529
kif11	0.107	0.172	0.172	0.363	0.245	0.299	0.461
kit	0.008	0.056	0.046	0.044	0.028	0.043	0.066
kith	0.130	0.141	0.157	0.203	0.202	0.198	0.383
kpcb	0.201	0.132	0.232	0.410	0.237	0.264	0.686
lck	0.013	0.032	0.062	0.115	0.008	0.061	0.094
lkha4	0.103	0.217	0.239	0.290	0.092	0.277	0.453
mapk2	0.075	0.293	0.316	0.394	0.219	0.332	0.600
mcr	0.087	0.111	0.045	0.107	0.287	0.087	0.237
met	0.349	0.394	0.369	0.392	0.481	0.376	0.461
mk01	0.067	0.152	0.164	0.180	0.093	0.165	0.338
mk10	0.031	0.078	0.112	0.092	0.057	0.135	0.128
mk14	0.163	0.144	0.141	0.184	0.110	0.137	0.183
mmp13	0.077	0.145	0.108	0.153	0.262	0.130	0.349
mp2k1	0.133	0.161	0.105	0.134	0.088	0.161	0.229
nos1	0.040	0.108	0.096	0.059	0.032	0.095	0.054
nram	0.303	0.305	0.238	0.321	0.028	0.262	0.362
pa2ga	0.044	0.138	0.119	0.141	0.180	0.166	0.405
parp1	0.163	0.339	0.305	0.308	0.166	0.316	0.403
pde5a	0.040	0.099	0.119	0.181	0.112	0.119	0.233
pgh1	0.041	0.176	0.221	0.200	0.109	0.204	0.159
pgh2	0.114	0.367	0.345	0.474	0.194	0.382	0.515
plk1	0.010	0.018	0.035	0.044	0.121	0.060	0.064
pnph	0.133	0.188	0.256	0.561	0.273	0.333	0.729
ppara	0.362	0.289	0.342	0.336	0.181	0.341	0.381
ppard	0.102	0.174	0.124	0.129	0.023	0.169	0.301
pparg	0.227	0.139	0.134	0.182	0.006	0.186	0.340
prgr	0.143	0.168	0.170	0.122	0.121	0.221	0.182

Target					Color	Color	Color
	USR	VAMS	Unopt ROCS	Opt ROCS	USR	Unopt ROCS	Opt Rocs
ptn1	0.029	0.055	0.056	0.053	0.012	0.056	0.054
pur2	0.288	0.244	0.240	0.271	0.472	0.327	0.621
pygm	0.058	0.018	0.017	0.030	0.095	0.025	0.007
pyrd	0.314	0.567	0.589	0.640	0.014	0.566	0.623
reni	0.167	0.186	0.187	0.229	0.239	0.224	0.310
rock1	0.038	0.068	0.046	0.034	0.042	0.109	0.074
rxra	0.036	0.105	0.038	0.214	0.039	0.196	0.679
sahh	0.329	0.159	0.202	0.630	0.746	0.321	0.983
src	0.050	0.062	0.069	0.112	0.055	0.079	0.120
tgfr1	0.168	0.375	0.366	0.416	0.179	0.329	0.384
thb	0.139	0.359	0.426	0.558	0.092	0.443	0.697
thrb	0.079	0.031	0.035	0.035	0.083	0.033	0.076
try1	0.159	0.157	0.128	0.085	0.286	0.126	0.117
tryb1	0.030	0.061	0.066	0.026	0.058	0.110	0.135
tysy	0.289	0.217	0.155	0.138	0.484	0.254	0.264
urok	0.059	0.052	0.062	0.113	0.151	0.058	0.207
vgfr2	0.122	0.094	0.110	0.152	0.051	0.121	0.201
wee1	0.068	0.376	0.380	0.640	0.325	0.411	0.959
xiap	0.113	0.065	0.062	0.183	0.602	0.136	0.709
Average	0.106	0.157	0.162	0.216	0.166	0.187	0.326

**Table S3:** Corrected partial AUCs calculated at a false positive rate of 10% for various shape-based virtual screening algorithms. A value of 0.5 indicates random performance while a value of one indicates perfect classification for the initial fraction of the dataset that yields a 10% false positive rate. Calculations were performed using the pROC R library<sup>40</sup>.

Target					Color	Color	Color
	USR	VAMS	Unopt ROCS	Opt ROCS	USR	Unopt ROCS	Opt Rocs
aa2ar	0.520	0.528	0.534	0.559	0.491	0.551	0.615
abl1	0.496	0.520	0.528	0.553	0.515	0.544	0.594
ace	0.503	0.538	0.523	0.520	0.639	0.545	0.597
aces	0.478	0.479	0.481	0.499	0.483	0.486	0.514
ada	0.511	0.518	0.546	0.564	0.632	0.575	0.824
ada17	0.506	0.520	0.509	0.507	0.520	0.520	0.587
adrb1	0.497	0.527	0.528	0.525	0.509	0.528	0.564
adrb2	0.505	0.525	0.520	0.520	0.501	0.524	0.536
akt1	0.489	0.487	0.487	0.485	0.498	0.489	0.505
akt2	0.508	0.502	0.516	0.526	0.551	0.516	0.543
aldr	0.510	0.571	0.606	0.595	0.474	0.621	0.695
ampc	0.498	0.601	0.563	0.619	0.688	0.578	0.711
andr	0.514	0.545	0.528	0.551	0.616	0.554	0.633
aofb	0.495	0.504	0.507	0.505	0.502	0.499	0.498
bace1	0.488	0.481	0.481	0.484	0.481	0.481	0.495
braf	0.517	0.557	0.552	0.616	0.567	0.559	0.636
cah2	0.488	0.499	0.505	0.501	0.491	0.498	0.545
casp3	0.504	0.503	0.503	0.495	0.581	0.504	0.514
cdk2	0.526	0.568	0.584	0.602	0.602	0.588	0.605
comt	0.513	0.555	0.534	0.595	0.629	0.570	0.867
cp2c9	0.492	0.520	0.505	0.517	0.502	0.502	0.510
cp3a4	0.511	0.520	0.517	0.536	0.504	0.504	0.499
csf1r	0.554	0.621	0.612	0.631	0.529	0.619	0.633
cxcr4	0.484	0.555	0.576	0.723	0.528	0.622	0.731
def	0.526	0.593	0.597	0.662	0.644	0.609	0.761
dhi1	0.504	0.574	0.562	0.604	0.502	0.564	0.607
dpp4	0.539	0.553	0.572	0.559	0.586	0.590	0.603
drd3	0.485	0.492	0.497	0.490	0.479	0.493	0.489
dyr	0.495	0.505	0.498	0.512	0.669	0.567	0.710
egfr	0.499	0.542	0.560	0.566	0.512	0.583	0.675
esr1	0.518	0.599	0.626	0.646	0.637	0.643	0.743
esr2	0.520	0.551	0.554	0.625	0.691	0.597	0.714
fa10	0.521	0.540	0.539	0.561	0.538	0.547	0.633
fa7	0.525	0.494	0.509	0.520	0.706	0.511	0.584
fabp4	0.655	0.569	0.627	0.700	0.474	0.635	0.681
fak1	0.498	0.561	0.613	0.709	0.540	0.625	0.921
fgfr1	0.490	0.501	0.493	0.490	0.477	0.501	0.499

Target	USR	VAMS	Unopt ROCS	Opt ROCS	Color USR	Color Unopt ROCS	Color Opt Rocs
fkbl1a	0.501	0.523	0.515	0.534	0.479	0.506	0.512
fnta	0.532	0.520	0.504	0.540	0.548	0.511	0.646
fpps	0.646	0.838	0.824	0.846	0.570	0.843	0.964
gcr	0.517	0.535	0.517	0.548	0.539	0.521	0.552
glcm	0.500	0.507	0.525	0.521	0.538	0.531	0.558
gria2	0.540	0.518	0.565	0.654	0.548	0.562	0.675
grik1	0.501	0.519	0.553	0.550	0.485	0.550	0.600
hdac2	0.491	0.525	0.526	0.512	0.490	0.518	0.521
hdac8	0.499	0.504	0.502	0.533	0.722	0.510	0.634
hivint	0.484	0.498	0.501	0.533	0.474	0.493	0.508
hivpr	0.635	0.612	0.604	0.584	0.559	0.628	0.558
hivrt	0.546	0.540	0.561	0.520	0.552	0.550	0.541
hmdh	0.598	0.662	0.663	0.759	0.606	0.666	0.845
hs90a	0.522	0.580	0.562	0.604	0.555	0.565	0.705
hvk4	0.517	0.590	0.599	0.661	0.685	0.610	0.728
igflr	0.493	0.492	0.503	0.539	0.545	0.515	0.562
inha	0.486	0.523	0.523	0.602	0.545	0.538	0.635
ital	0.511	0.557	0.547	0.551	0.474	0.545	0.550
jak2	0.490	0.581	0.579	0.657	0.518	0.593	0.742
kif11	0.528	0.557	0.552	0.666	0.599	0.625	0.715
kit	0.477	0.500	0.494	0.494	0.486	0.492	0.504
kith	0.528	0.537	0.543	0.569	0.568	0.563	0.663
kpcb	0.580	0.535	0.587	0.673	0.592	0.601	0.821
lck	0.479	0.488	0.501	0.530	0.476	0.502	0.518
lkha4	0.527	0.579	0.594	0.617	0.516	0.615	0.704
mapk2	0.507	0.615	0.630	0.672	0.579	0.639	0.775
mcr	0.516	0.522	0.492	0.521	0.613	0.508	0.586
met	0.656	0.680	0.673	0.687	0.729	0.679	0.701
mk01	0.505	0.547	0.552	0.566	0.513	0.556	0.629
mk10	0.487	0.512	0.525	0.516	0.497	0.539	0.533
mk14	0.557	0.546	0.542	0.566	0.527	0.540	0.564
mmp13	0.509	0.545	0.525	0.547	0.607	0.536	0.648
mp2k1	0.537	0.554	0.525	0.541	0.520	0.551	0.587
nos1	0.493	0.528	0.523	0.504	0.490	0.526	0.500
nram	0.622	0.635	0.592	0.648	0.485	0.605	0.659
pa2ga	0.489	0.538	0.528	0.538	0.561	0.554	0.679
parp1	0.552	0.643	0.625	0.625	0.555	0.631	0.672
pde5a	0.491	0.520	0.532	0.561	0.526	0.530	0.582
pgh1	0.492	0.561	0.589	0.570	0.529	0.578	0.549
pgh2	0.527	0.656	0.644	0.717	0.562	0.661	0.729
plk1	0.478	0.480	0.486	0.490	0.536	0.500	0.501
pnph	0.539	0.566	0.604	0.758	0.606	0.646	0.855
ppara	0.661	0.619	0.650	0.649	0.562	0.649	0.663



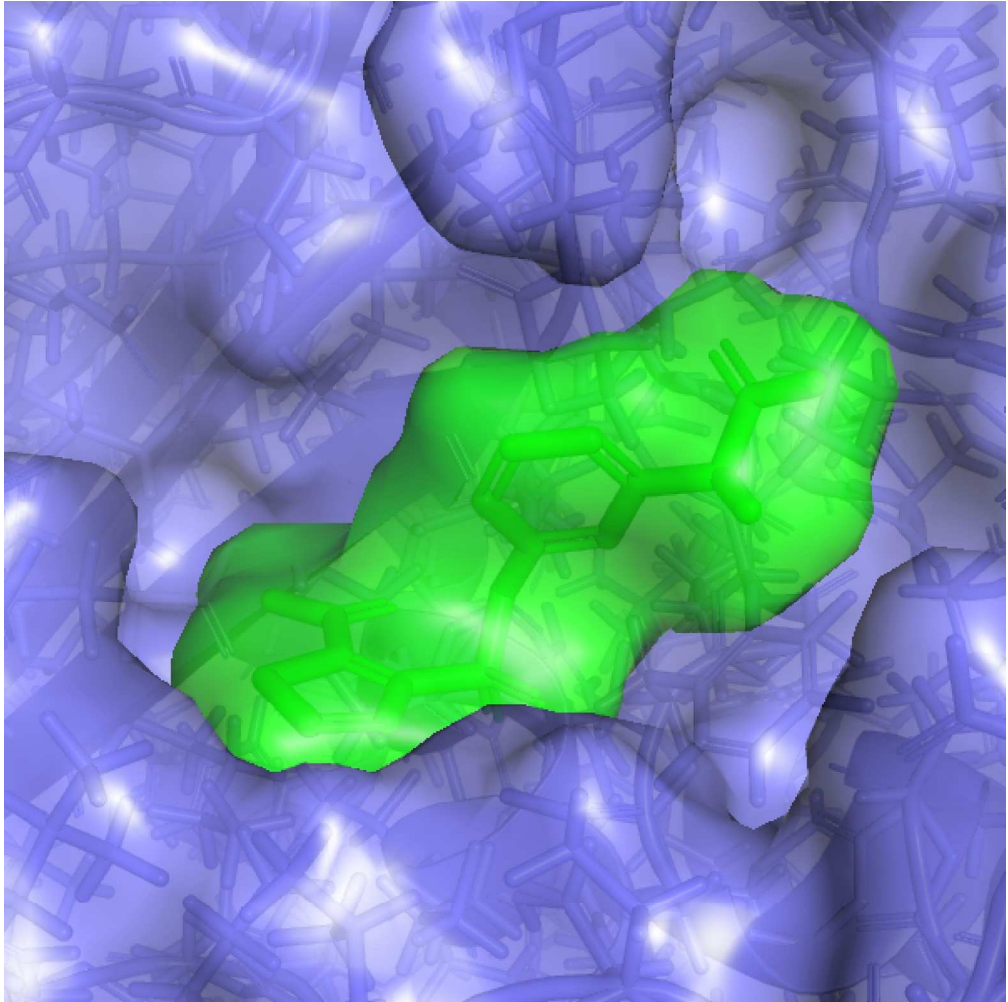
Target					Color	Color	Color
	USR	VAMS	Unopt ROCS	Opt ROCS	USR	Unopt ROCS	Opt Rocs
ppard	0.520	0.560	0.532	0.532	0.483	0.555	0.632
pparg	0.588	0.541	0.535	0.560	0.476	0.563	0.640
prgr	0.538	0.553	0.559	0.528	0.527	0.586	0.559
ptn1	0.489	0.498	0.499	0.498	0.480	0.499	0.499
pur2	0.621	0.587	0.583	0.602	0.709	0.637	0.795
pygm	0.503	0.477	0.481	0.488	0.515	0.487	0.476
pyrd	0.619	0.756	0.775	0.801	0.477	0.748	0.780
reni	0.555	0.563	0.566	0.588	0.591	0.580	0.624
rock1	0.490	0.507	0.495	0.487	0.489	0.533	0.503
rxra	0.488	0.521	0.489	0.576	0.490	0.567	0.833
sahh	0.638	0.551	0.568	0.797	0.864	0.623	0.990
src	0.492	0.499	0.503	0.527	0.498	0.508	0.532
tgfr1	0.554	0.663	0.658	0.679	0.557	0.641	0.670
thb	0.538	0.655	0.690	0.761	0.511	0.700	0.838
thrb	0.506	0.485	0.489	0.489	0.512	0.487	0.507
try1	0.547	0.550	0.535	0.513	0.614	0.535	0.529
tryb1	0.487	0.503	0.505	0.482	0.500	0.525	0.538
tysy	0.628	0.585	0.555	0.537	0.723	0.607	0.607
urok	0.500	0.497	0.502	0.526	0.548	0.499	0.576
vgfr2	0.530	0.517	0.524	0.545	0.494	0.528	0.572
weel	0.505	0.653	0.654	0.796	0.646	0.675	0.977
xiap	0.523	0.498	0.500	0.560	0.778	0.539	0.849
Average	0.524	0.550	0.553	0.581	0.555	0.565	0.637

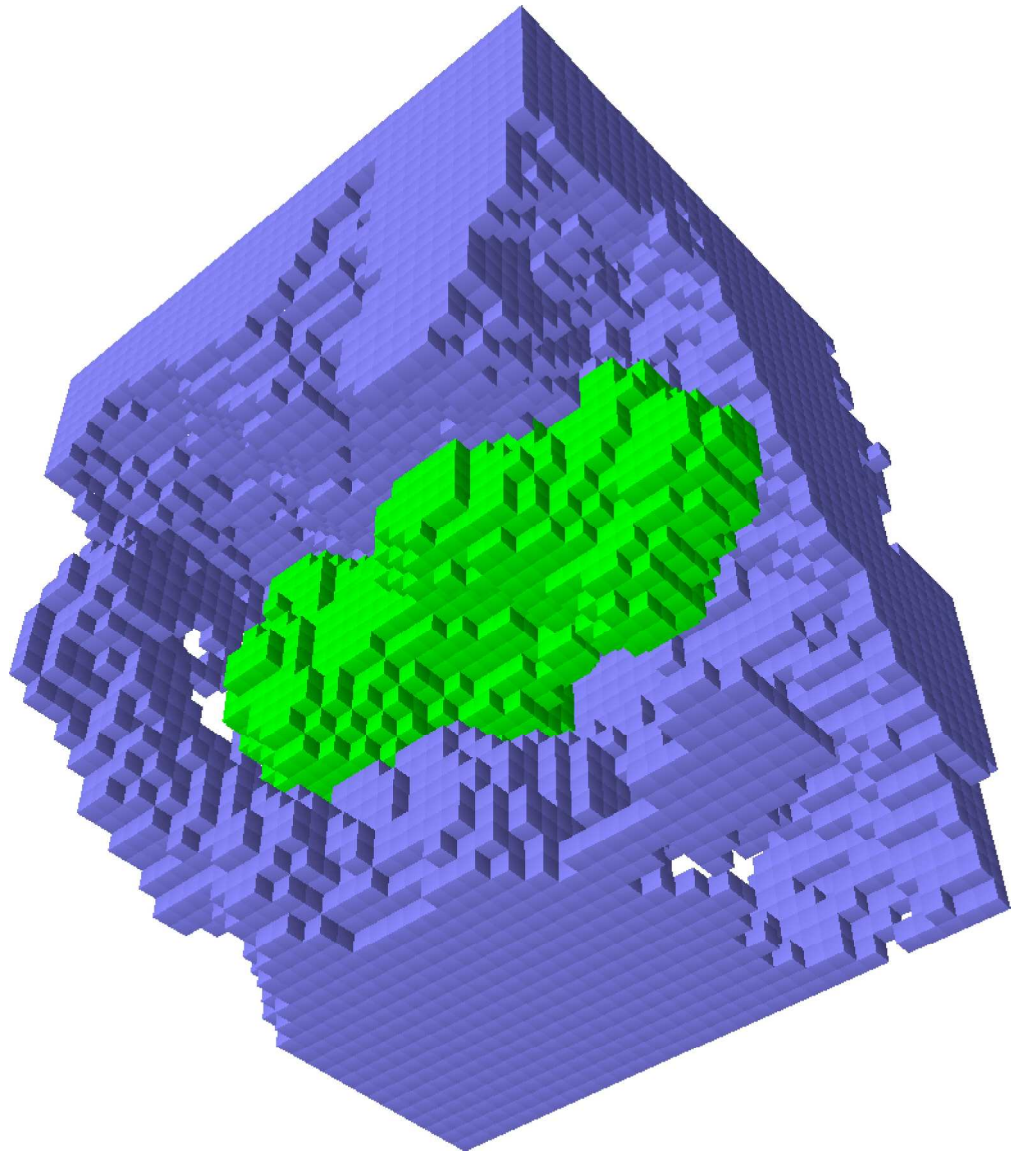
**Table S4:** Screening results for minimum/maximum shape constraints. Both ligand only and ligand-receptor shape constraints were considered with shrinking/growing gap sizes of 1, 1.5, and 2Å resulting in a total of 18 searches for every DUD-E target. For each target, only the result with the highest F1 score is shown. The  $p$ -value of enrichment is computed using the hypergeometric distribution and is shown in bold if it is statistically significant after the Bonferroni correction for multiple comparisons ( $p < 0.05/18$ ). LO: Ligand only shape constraint. LR: Ligand-receptor shape constraint. TP: True Positives. FP: False Positives. FN: False Negatives. TN: True Negatives. EF: Enrichment Factor.

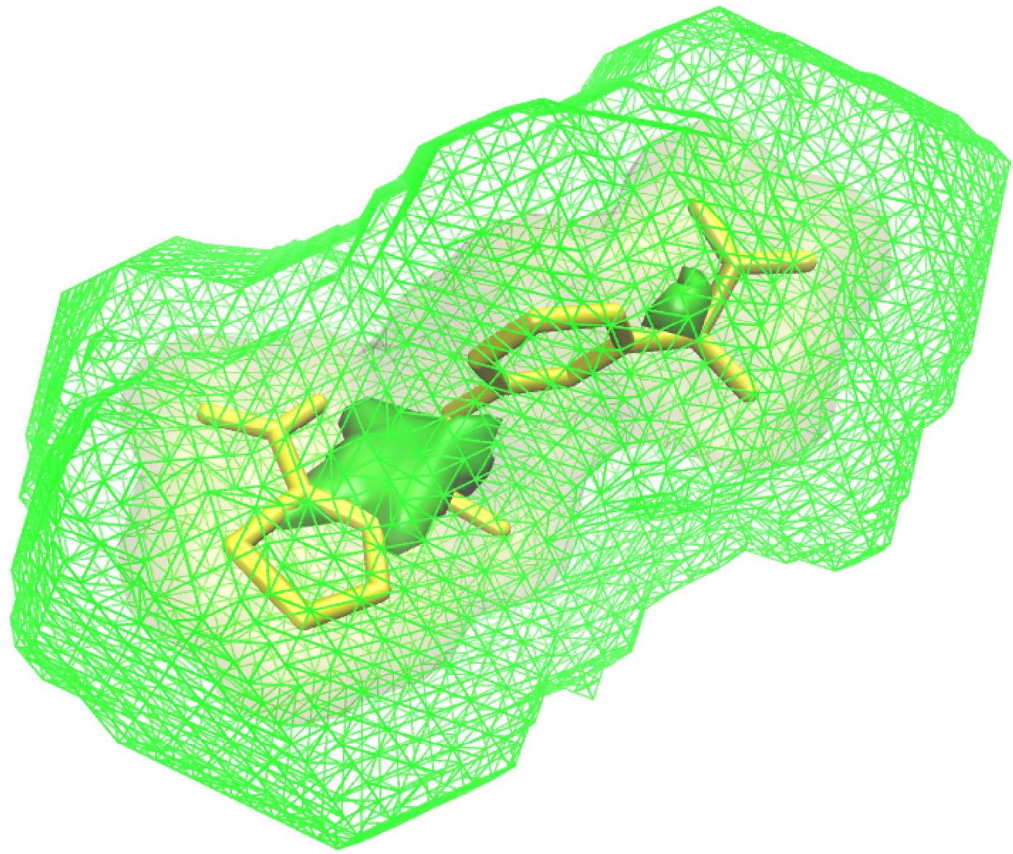
Target	Constraint	Shrink	Grow	TP	FP	FN	TN	EF	$p$
aa2ar	LR	1.0	1.5	31	735	451	30758	2.685	<b>2.72543e-07</b>
abl1	LR	1.0	2.0	11	299	171	10447	2.131	0.00569147
ace	LR	2.0	2.0	6	361	276	16497	0.994	0.399905
aces	LR	1.0	2.0	19	1354	434	24880	0.815	0.790005
ada	LR	1.0	2.0	4	16	89	5433	11.918	<b>1.5175e-05</b>
ada17	LR	2.0	2.0	194	9594	338	26212	1.354	<b>4.98664e-07</b>
adrb1	LR	2.0	1.5	23	558	224	15284	2.579	<b>1.0897e-05</b>
adrb2	LR	2.0	1.5	8	131	223	14861	3.793	<b>0.000271003</b>
akt1	LR	2.0	1.0	4	9	289	16417	17.557	<b>1.83249e-06</b>
akt2	LR	2.0	1.5	6	58	111	6835	5.617	<b>8.52755e-05</b>
aldr	LR	2.0	2.0	92	4473	67	4520	1.160	0.0172504
ampc	LR	1.0	1.5	6	33	42	2814	9.279	<b>2.25987e-06</b>
andr	LR	1.0	1.0	7	0	262	14341	54.312	<b>0</b>
aofb	LR	1.0	1.5	16	702	106	6195	1.282	0.115413
bace1	LR	2.0	2.0	61	6303	222	11777	0.622	0.999999
braf	LR	1.0	1.5	17	38	135	9906	20.530	<b>0</b>
cah2	LR	1.0	1.5	4	49	488	31082	4.851	<b>0.0013865</b>
casp3	LR	2.0	1.5	34	1544	165	9147	1.179	0.126063
cdk2	LR	2.0	2.0	58	1087	416	26742	3.025	<b>1.95399e-14</b>
comt	LR	1.0	1.0	1	11	40	3837	7.904	0.00669518
cp2c9	LR	1.0	2.0	3	17	117	7426	9.454	<b>0.000239934</b>
cp3a4	LR	1.0	0.5	0	0	170	11793	0.000	<b>0</b>
csf1r	LR	1.0	1.5	24	9	142	12135	53.932	<b>0</b>
cxcr4	LR	2.0	2.0	12	336	28	3070	2.971	<b>8.66808e-05</b>
def	LR	1.0	2.0	8	46	94	5650	8.421	<b>3.11867e-07</b>
dhi1	LR	2.0	2.0	90	2955	239	16382	1.767	<b>9.47984e-09</b>
dpp4	LR	2.0	1.5	51	776	482	40137	4.795	<b>0</b>
drd3	LR	2.0	2.0	119	11871	361	22149	0.713	0.999999
dyr	LR	2.0	2.0	110	10752	121	6418	0.763	0.999997
egfr	LR	2.0	2.0	129	4506	413	30515	1.826	<b>2.14273e-12</b>
esr1	LR	2.0	1.5	20	13	363	20649	33.302	<b>0</b>

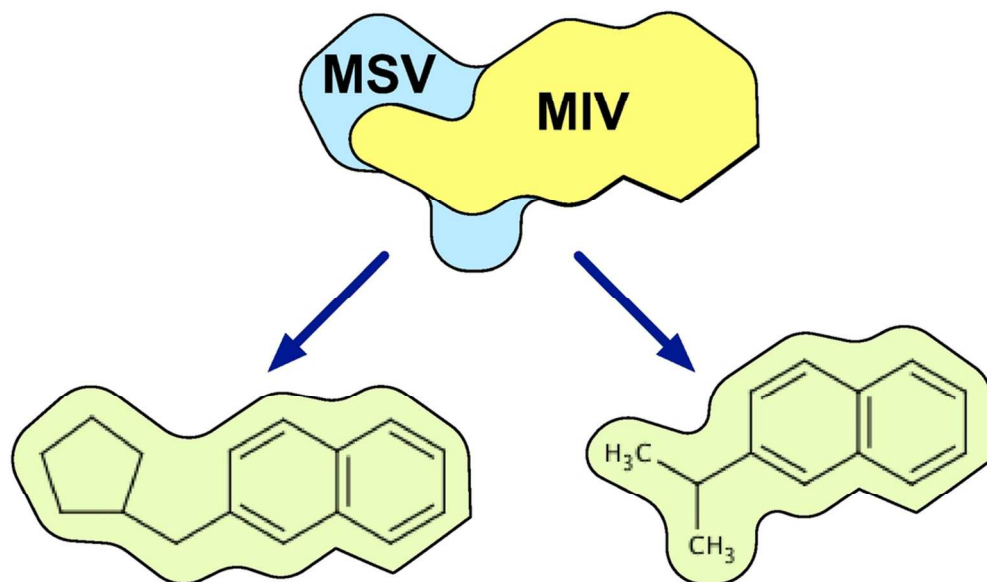
Target	Constraint	Shrink	Grow	TP	FP	FN	TN	EF	$p$
esr2	LR	2.0	1.5	23	81	344	20101	12.383	<b>0</b>
fa10	LR	2.0	2.0	207	7608	330	20638	1.420	<b>2.63255e-09</b>
fa7	LR	1.0	0.5	0	0	114	6245	0.000	<b>0</b>
fabp4	LR	2.0	2.0	3	79	44	2670	2.176	0.047167
fak1	LR	2.0	1.5	4	7	96	5343	19.818	<b>7.96567e-07</b>
fgfr1	LR	2.0	2.0	28	1499	111	7192	1.165	0.156432
fkbl1a	LR	2.0	2.0	14	421	97	5379	1.714	0.0153565
fnta	LR	2.0	2.0	19	1322	573	50090	1.245	0.135909
fpps	LR	1.0	1.0	12	4	73	8819	78.600	<b>0</b>
gcr	LR	2.0	2.0	55	3326	203	11657	0.961	0.598412
glcm	LR	1.0	1.5	4	27	50	3772	9.207	<b>5.7709e-05</b>
gria2	LR	1.0	2.0	9	156	149	11675	4.139	<b>6.45237e-05</b>
grik1	LR	2.0	1.5	11	143	90	6404	4.702	<b>3.13483e-06</b>
hdac2	LR	2.0	2.0	31	509	154	9791	3.254	<b>1.16764e-09</b>
hdac8	LR	2.0	2.0	12	305	158	10143	2.364	<b>0.00173738</b>
hivint	LR	2.0	1.5	6	288	94	6357	1.377	0.145247
hivpr	LR	2.0	2.0	68	1390	468	34296	3.152	<b>0</b>
hivrt	LR	2.0	2.0	176	3913	162	14962	2.447	<b>0</b>
hmdh	LR	2.0	2.0	99	1913	71	6830	2.580	<b>0</b>
hs90a	LR	2.0	1.0	4	4	84	4844	28.045	<b>8.6296e-08</b>
hvk4	LR	2.0	2.0	18	51	74	4647	13.582	<b>0</b>
igf1r	LR	2.0	2.0	73	7020	75	2271	0.656	1
inha	LR	2.0	1.0	3	0	40	2300	54.488	<b>0</b>
ital	LR	2.0	2.0	20	1089	118	7396	1.127	0.235465
jak2	LR	1.0	2.0	43	1742	64	4752	1.486	<b>0.0010306</b>
kif11	LR	2.0	2.0	71	2523	45	4326	1.643	<b>4.04692e-08</b>
kit	LR	2.0	2.0	5	95	161	10352	3.197	0.00475264
kith	LR	2.0	1.5	3	16	54	2834	8.053	<b>0.000413717</b>
kpcb	LR	2.0	2.0	44	1753	90	6928	1.611	<b>0.000223287</b>
lck	LR	2.0	2.0	15	1125	405	26249	0.871	0.654434
lkha4	LR	2.0	2.0	37	136	134	9313	12.032	<b>0</b>
mapk2	LR	1.0	1.5	11	33	90	6114	15.465	<b>2.24865e-12</b>
mcr	LR	1.0	1.5	2	4	92	5142	18.582	<b>0.000107549</b>
met	LR	2.0	2.0	14	137	152	11102	6.370	<b>4.80784e-09</b>
mk01	LR	2.0	1.0	4	60	75	4488	3.661	0.00443472
mk10	LR	2.0	2.0	3	106	101	6492	1.774	0.0887752
mk14	LR	2.0	2.0	66	3330	512	32479	1.223	0.0382502
mmp13	LR	2.0	2.0	87	2061	485	35064	2.669	<b>0</b>
mp2k1	LR	2.0	2.0	34	1197	87	6949	1.887	<b>5.0929e-05</b>
nos1	LR	1.0	2.0	7	162	93	7888	3.376	<b>0.00106647</b>
nram	LR	2.0	1.5	6	104	92	6095	3.505	<b>0.00153523</b>
pa2ga	LR	2.0	2.0	7	278	92	4869	1.302	0.168349
parp1	LR	1.0	1.5	63	245	445	29786	12.296	<b>0</b>
pde5a	LR	2.0	2.0	82	3673	316	23845	1.532	<b>2.67242e-05</b>

Target	Constraint	Shrink	Grow	TP	FP	FN	TN	EF	$p$
pgh1	LR	1.0	2.0	29	894	166	9901	1.771	<b>0.000842881</b>
pgh2	LR	2.0	1.5	70	529	365	22603	6.331	<b>0</b>
plk1	LR	2.0	2.0	47	3307	60	3490	0.904	0.80872
pnph	LR	2.0	1.5	10	218	93	6732	3.003	<b>0.000459765</b>
ppara	LR	2.0	2.0	138	1726	235	17632	3.916	<b>0</b>
ppard	LR	2.0	2.0	34	583	206	11641	2.862	<b>8.0168e-09</b>
pparg	LR	2.0	2.0	29	917	455	24338	1.630	0.00397403
prgr	LR	2.0	2.0	93	3902	200	11739	1.266	0.00384502
ptn1	LR	2.0	1.0	6	233	124	7010	1.424	0.128874
pur2	LR	2.0	2.0	3	66	47	2628	2.386	0.0353888
pygm	LR	2.0	2.0	62	3088	15	851	1.027	0.283901
pyrd	LR	2.0	1.0	24	3	87	6441	52.492	<b>0</b>
reni	LR	2.0	2.0	21	603	83	6352	2.284	<b>8.46454e-05</b>
rock1	LR	2.0	1.5	18	969	82	5328	1.167	0.193313
rxra	LR	2.0	2.0	58	3513	73	3420	0.876	0.913524
sahh	LR	2.0	1.0	8	34	55	3416	10.621	<b>2.99202e-08</b>
src	LR	2.0	2.0	123	7195	401	27260	1.122	0.068177
tgfr1	LR	1.0	1.5	28	63	105	8434	19.965	<b>0</b>
thb	LR	2.0	1.5	27	67	76	7372	21.032	<b>0</b>
thrb	LR	2.0	2.0	222	15840	239	11105	0.822	0.999997
try1	LR	2.0	2.0	114	5806	335	20108	1.131	0.0610022
tryb1	LR	2.0	2.0	14	920	134	6723	0.789	0.793576
tysy	LR	2.0	2.0	42	1113	67	5624	2.284	<b>1.35082e-08</b>
urok	LR	2.0	2.0	4	126	158	9715	1.900	0.059886
vgfr2	LR	2.0	2.0	141	6110	268	18816	1.397	<b>2.95124e-06</b>
weel	LR	2.0	1.5	25	4	77	6145	52.831	<b>0</b>
xiap	LR	2.0	2.0	5	148	95	4997	1.714	0.0709458

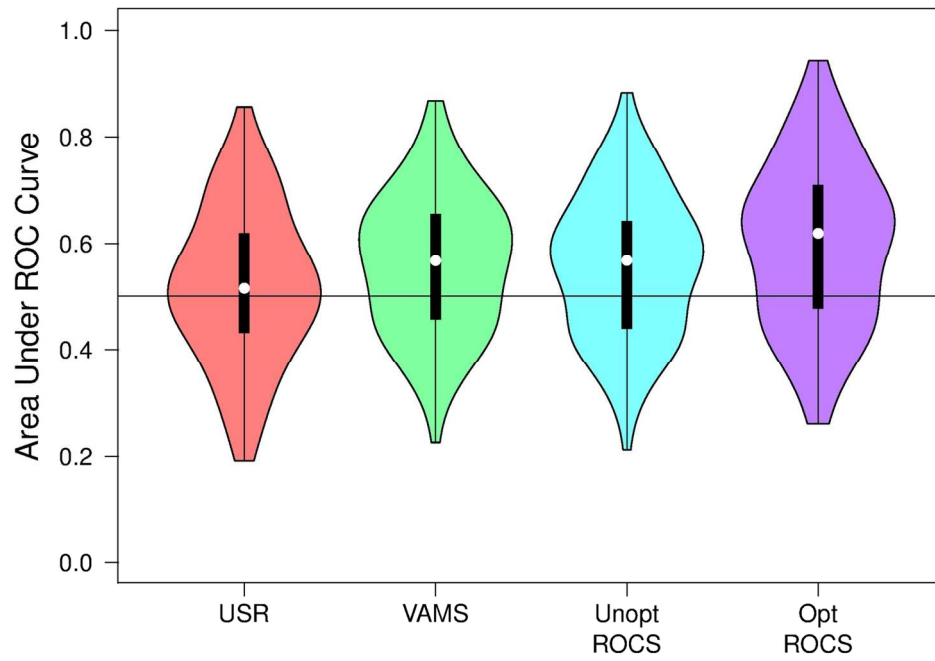


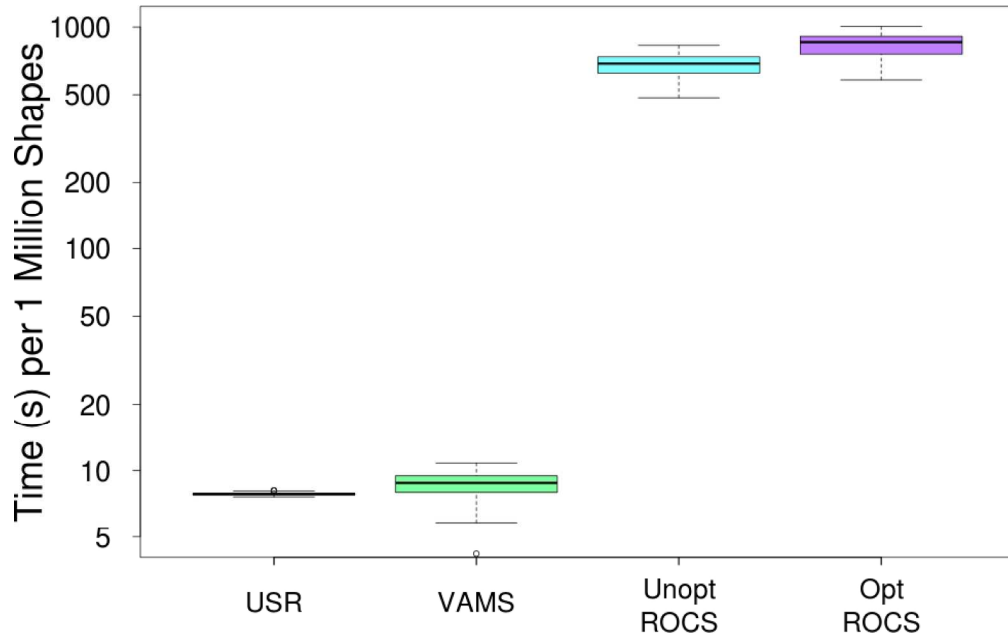


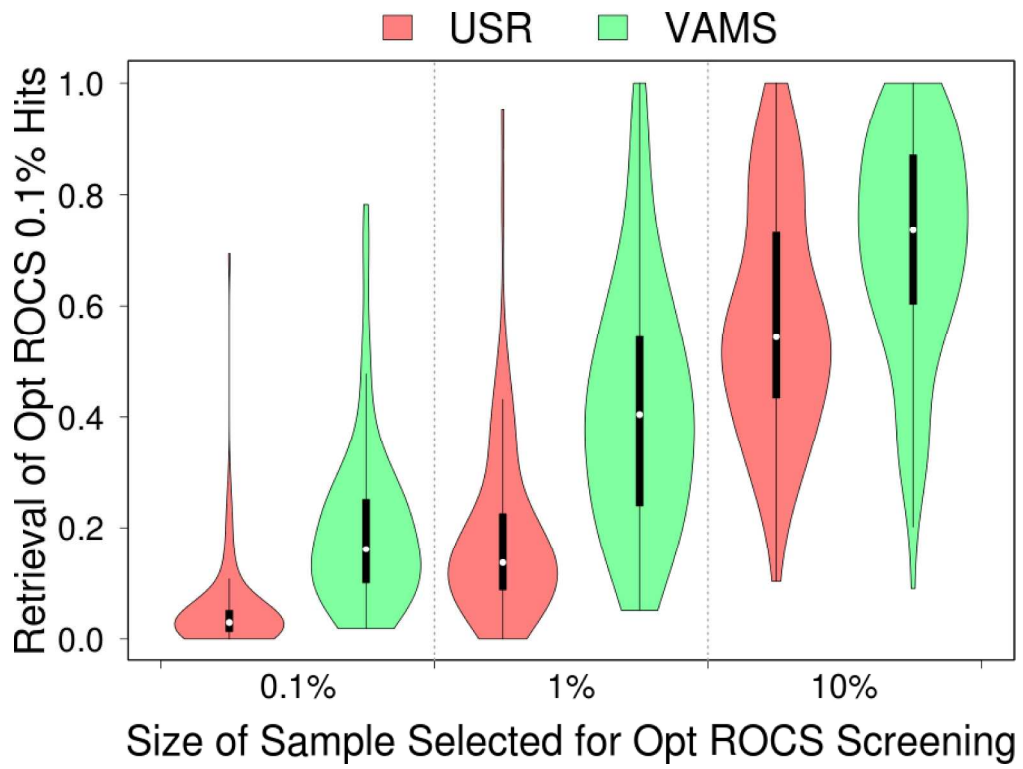


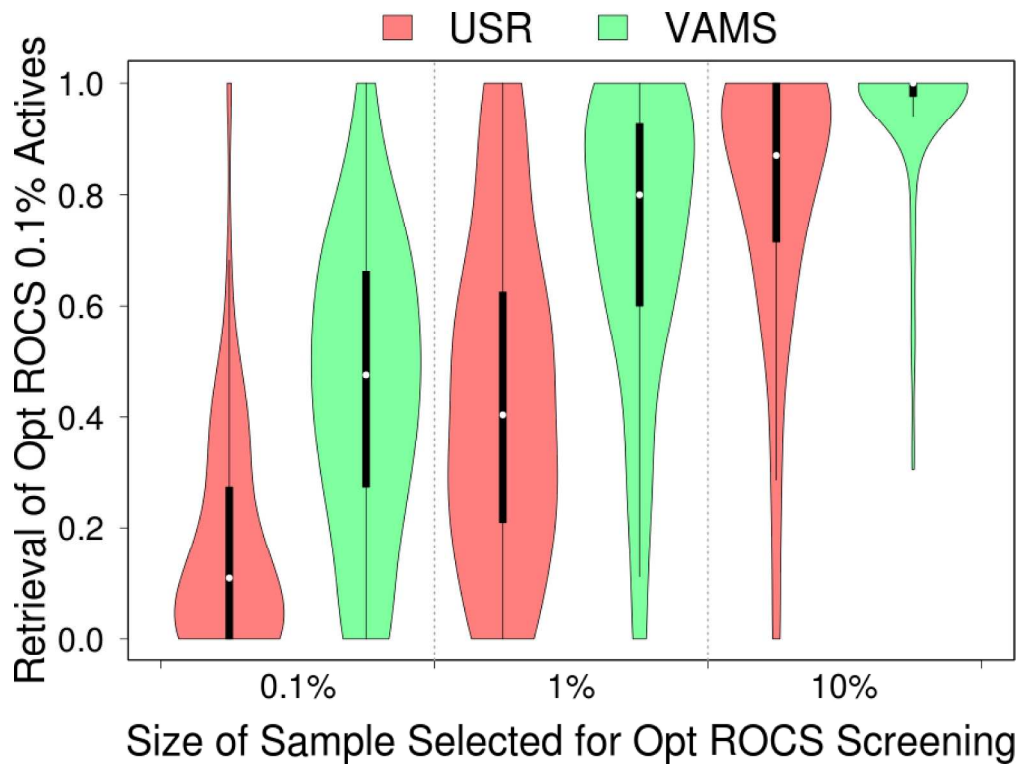






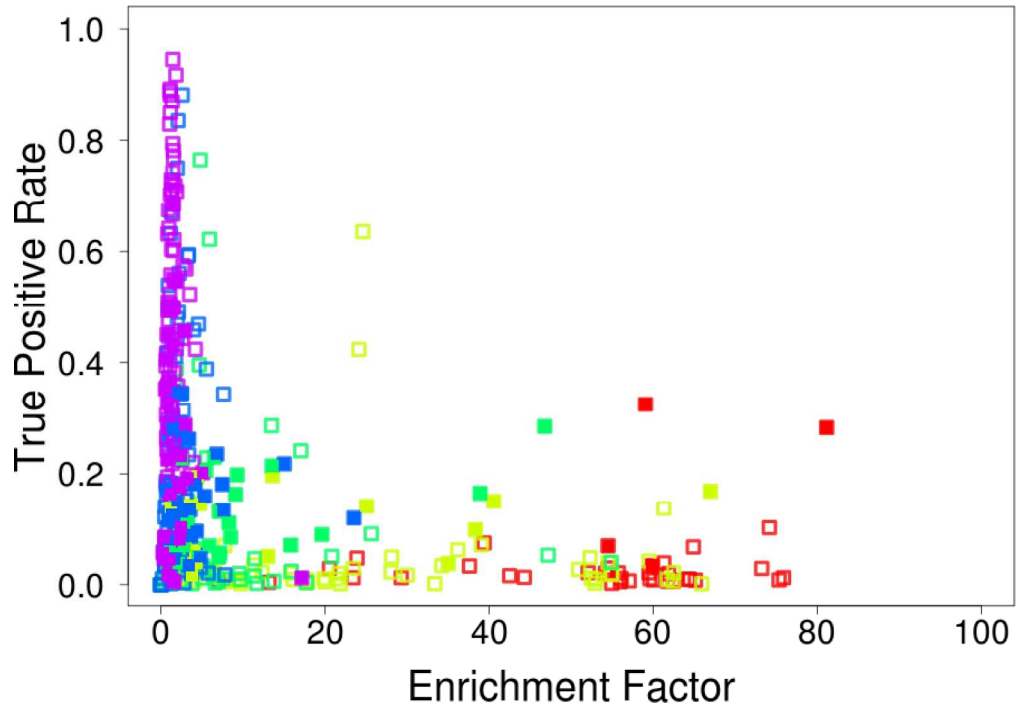


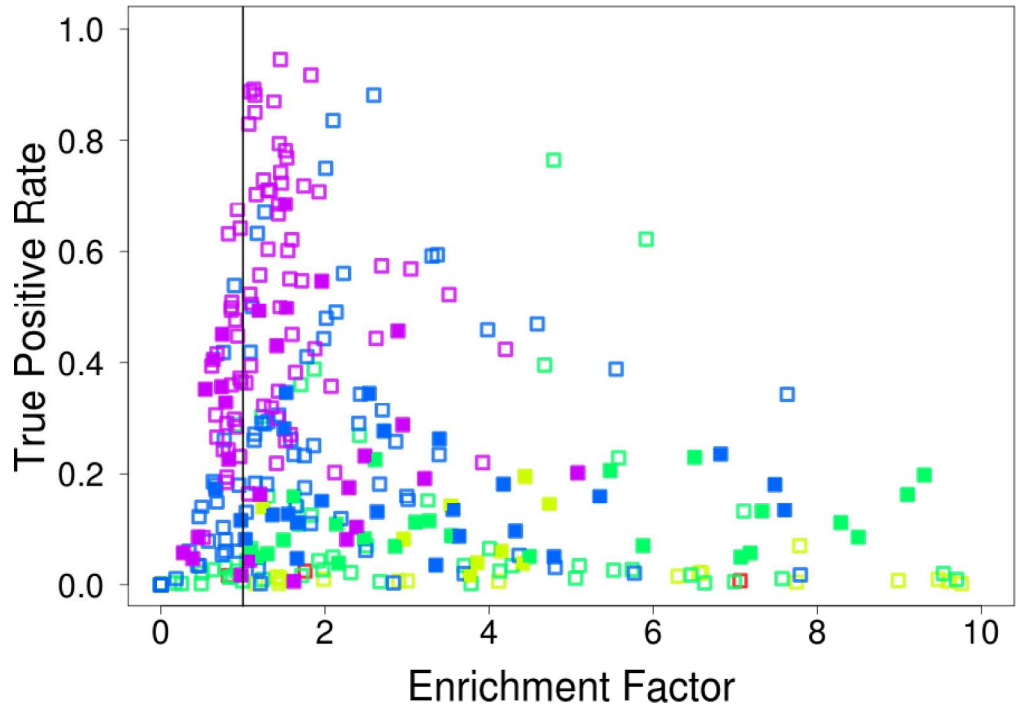


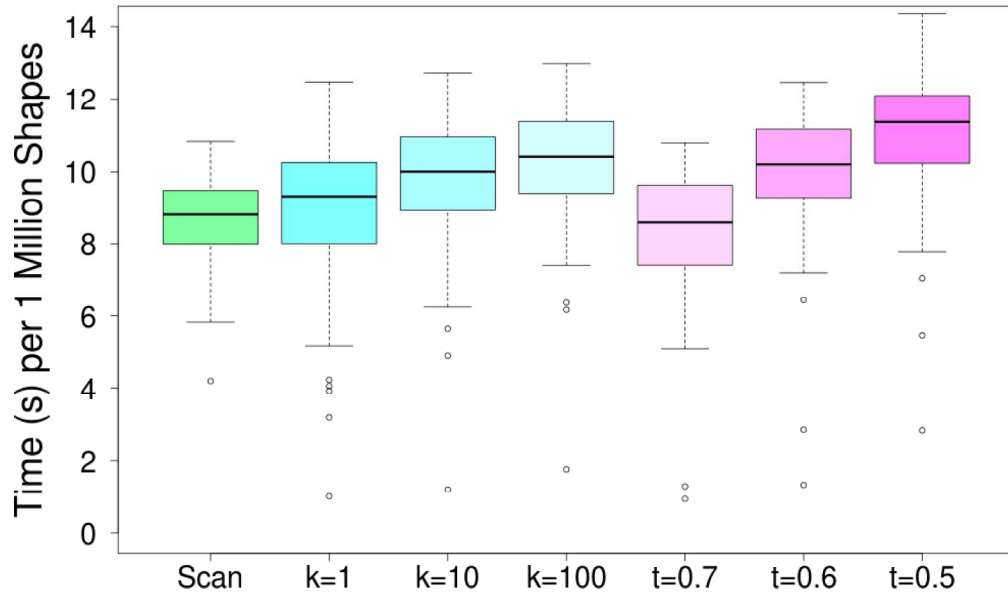


# Similarity Threshold

- 0.70
- 0.65
- 0.60
- 0.55
- 0.50



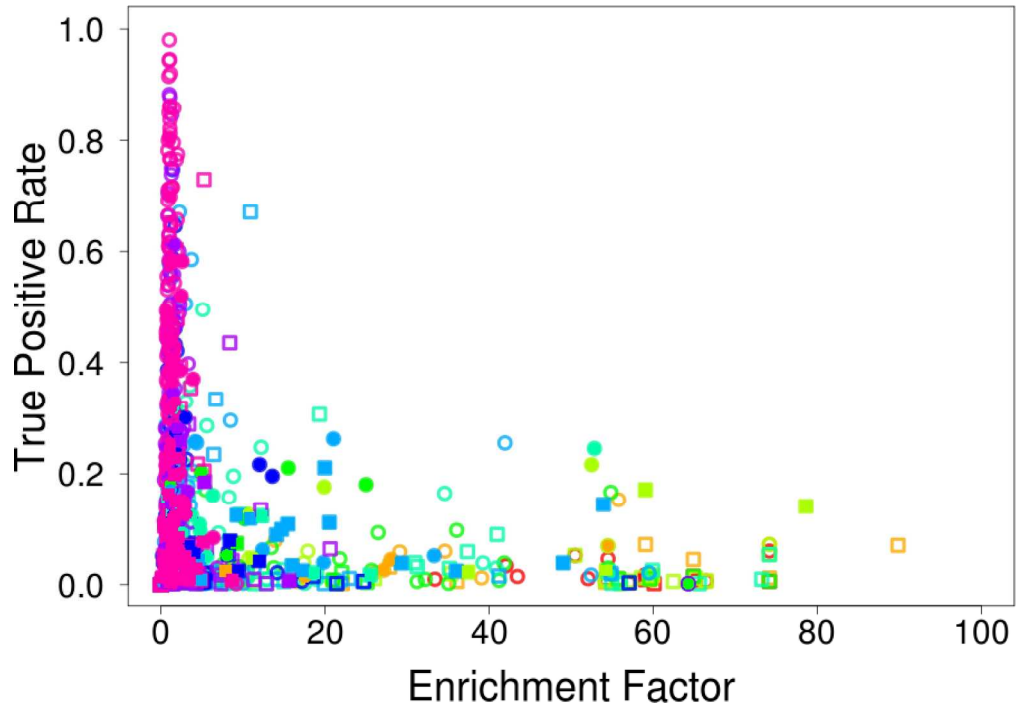


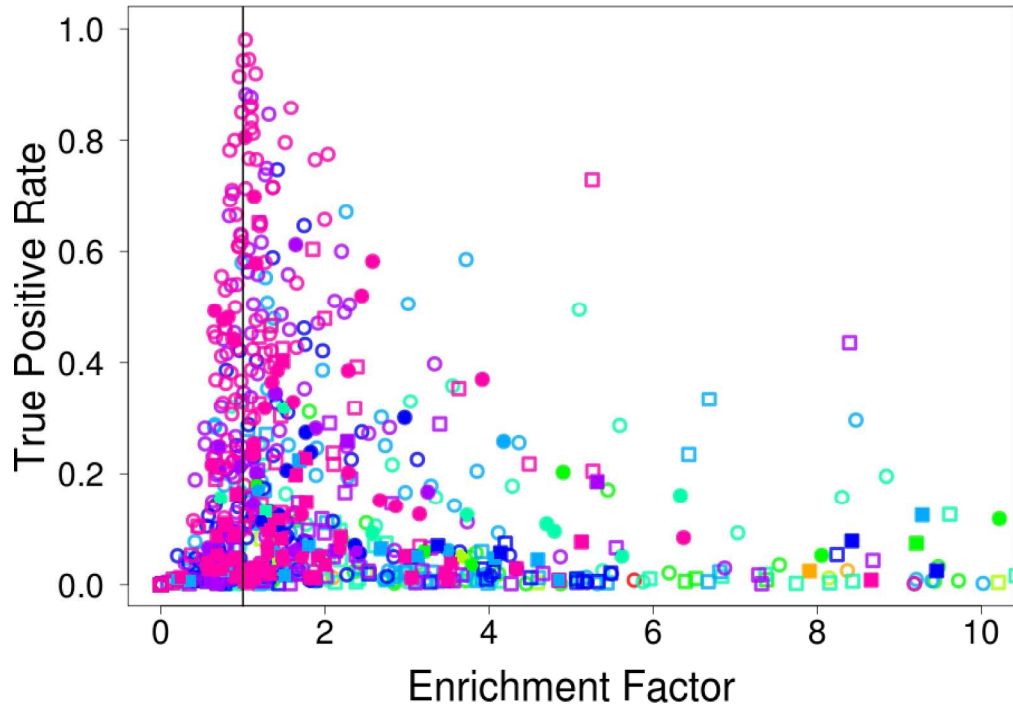




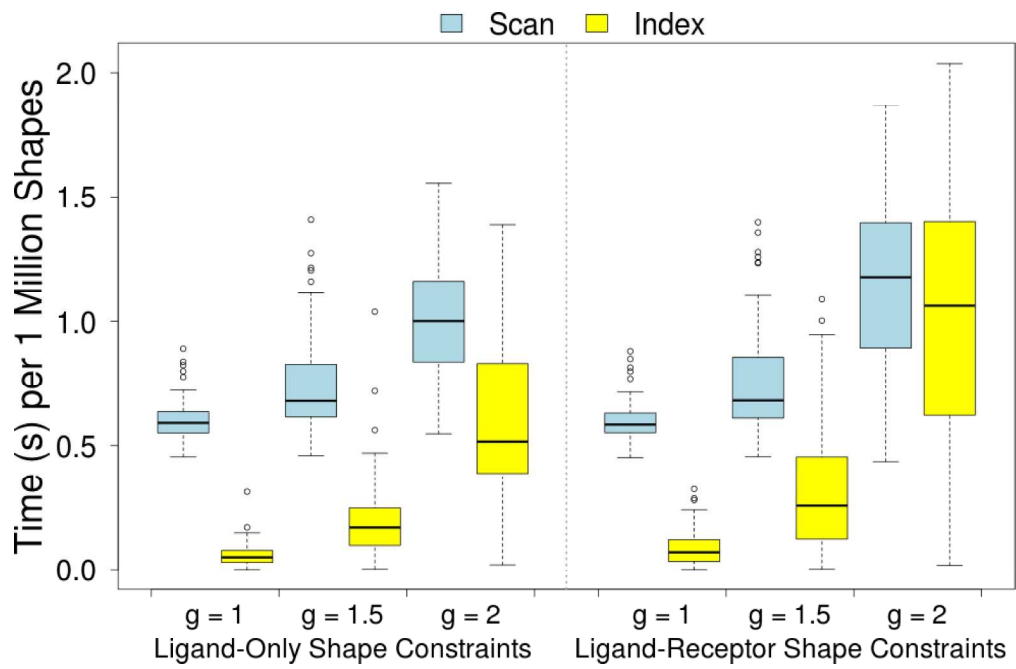
Gap Distance (Å)  
shrink grow

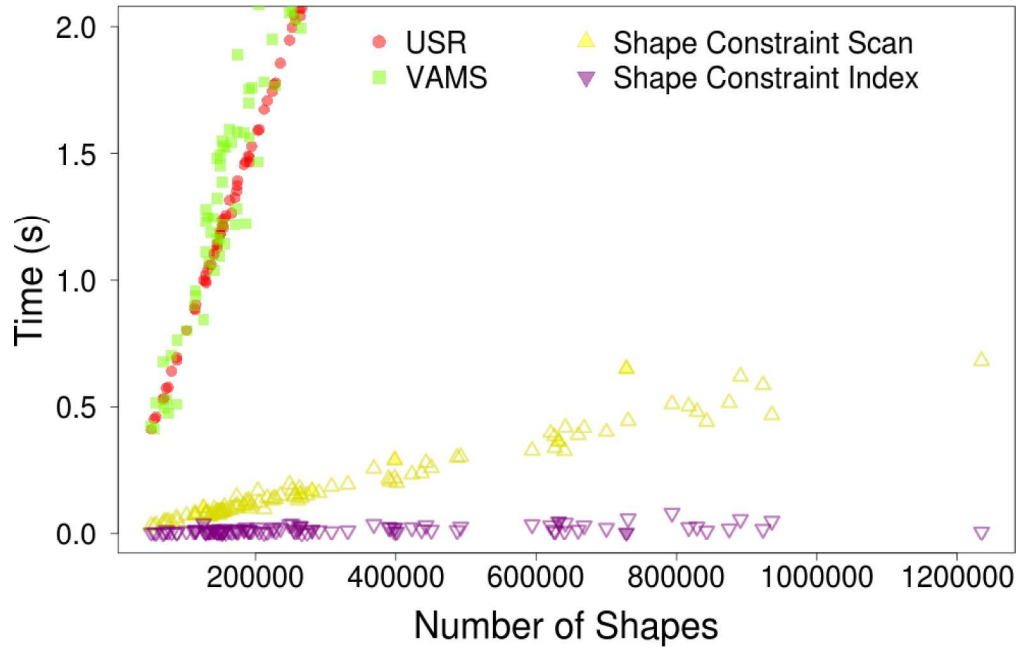
◆	1.0	1.0
◆	1.0	1.5
◆	1.0	2.0
◆	1.5	1.0
◆	1.5	1.5
◆	1.5	2.0
◆	2.0	1.0
◆	2.0	1.5
◆	2.0	2.0

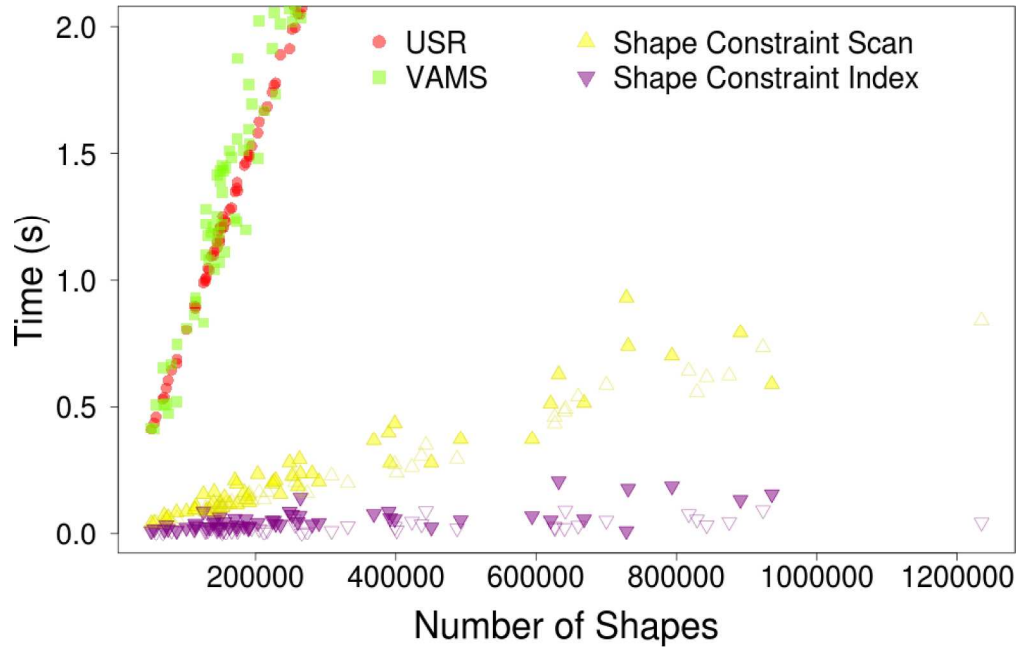


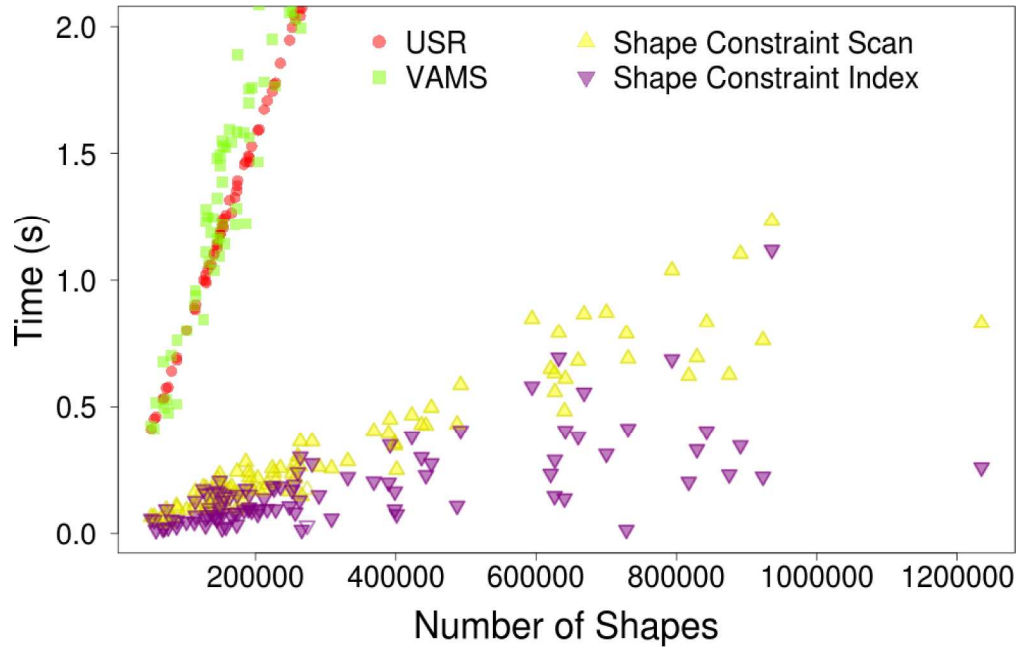


- Ligand Only
- Ligand-Receptor

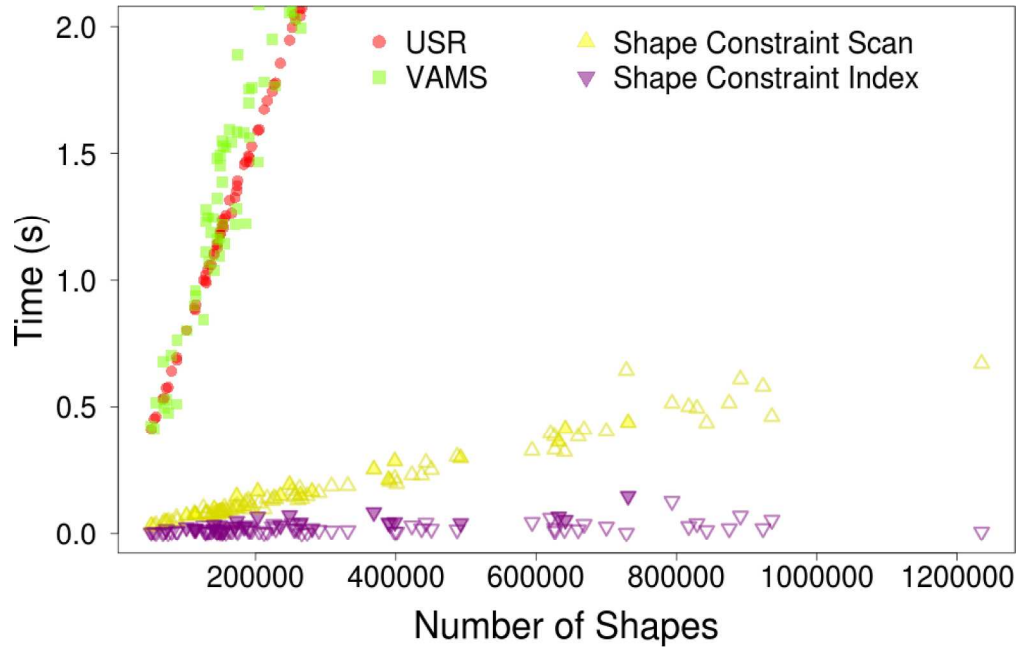


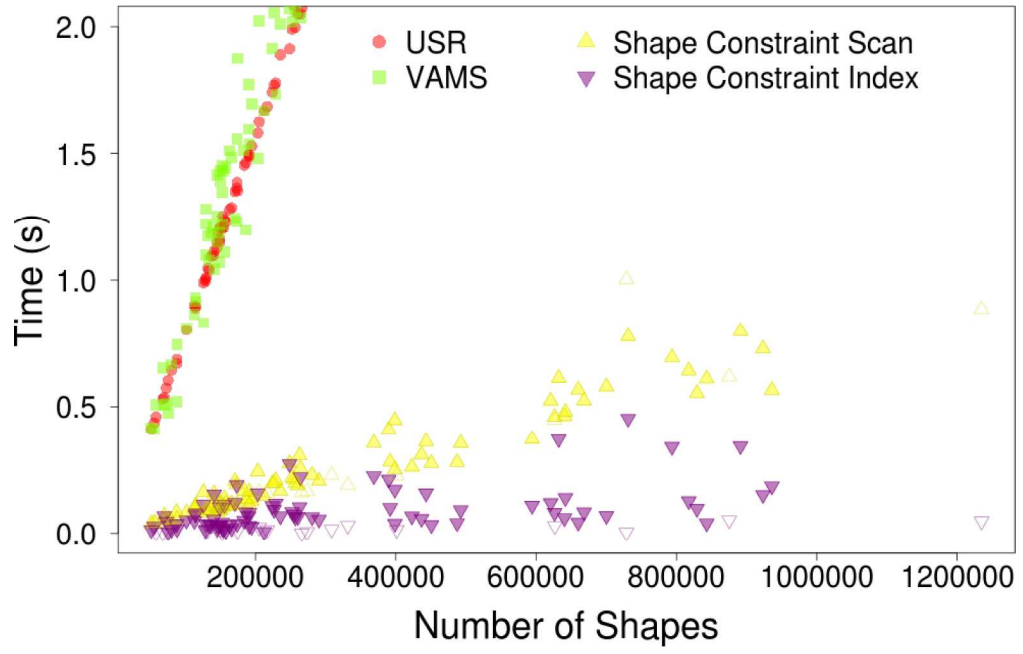


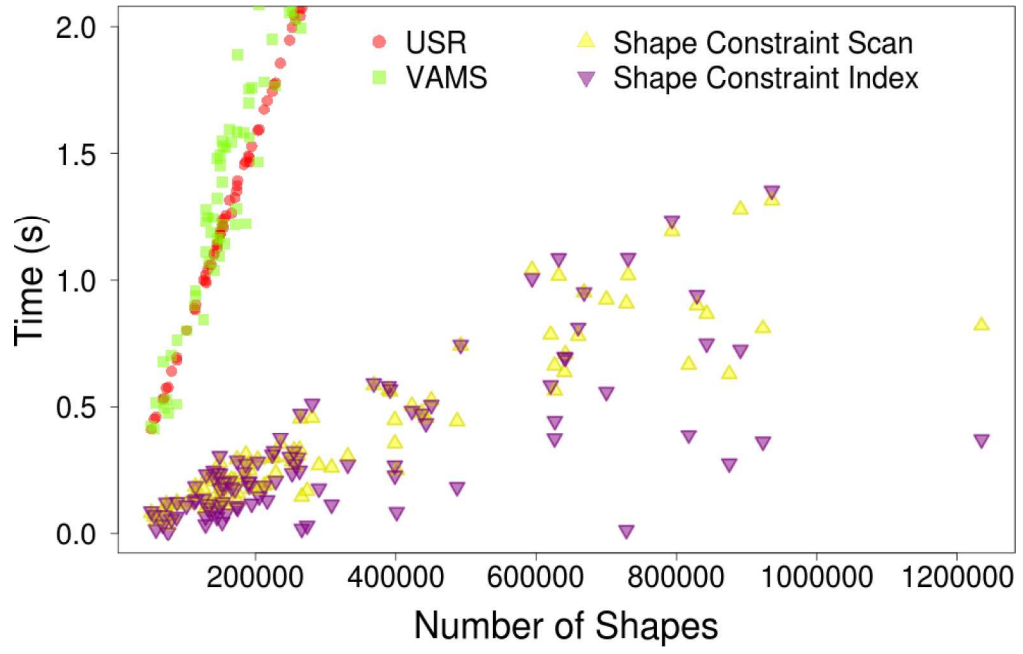


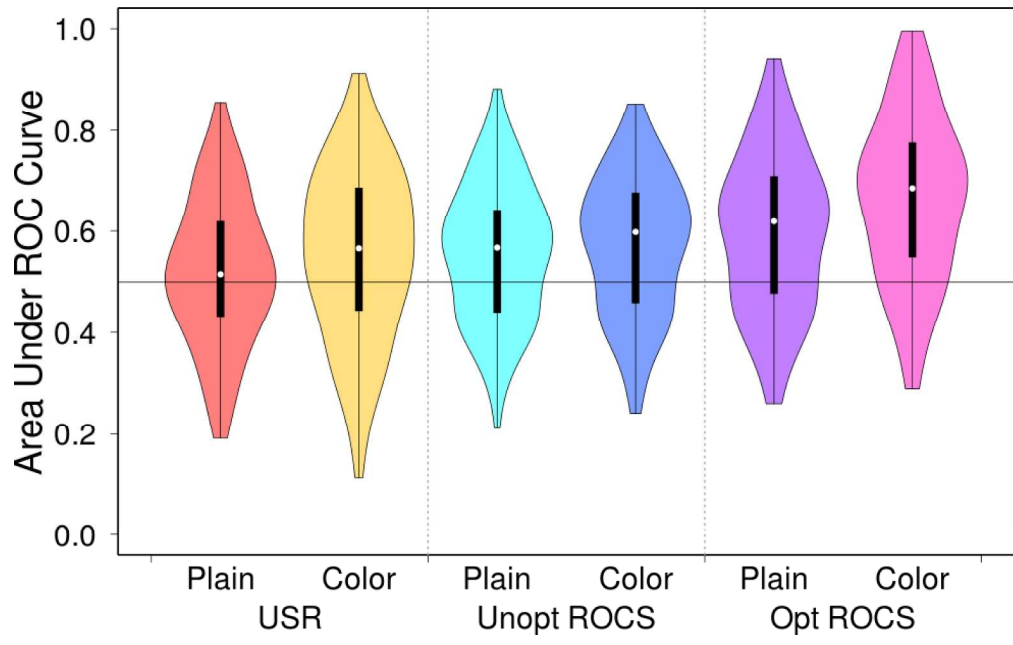


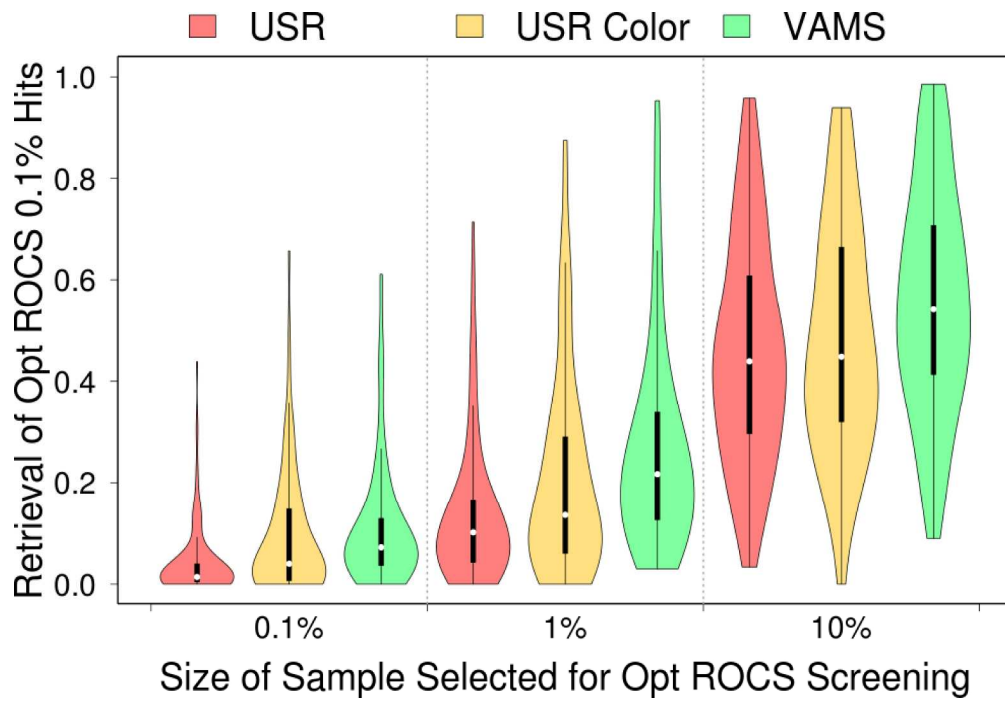


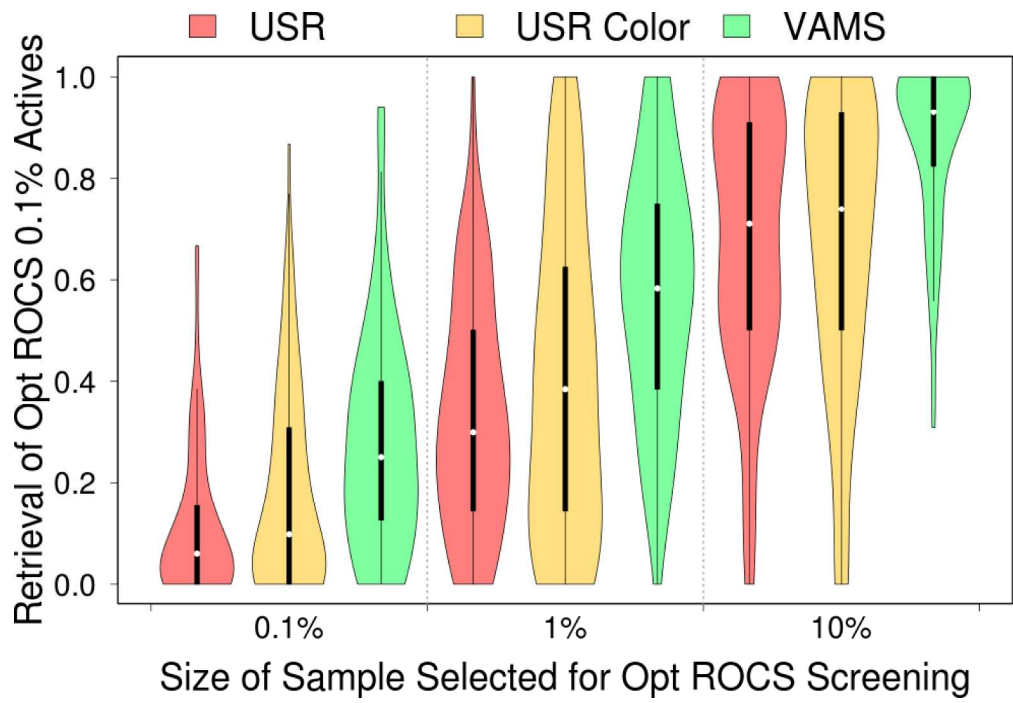












Volumetric aligned molecular shapes provide a way to screen libraries of molecular shapes that approaches the speed of the fastest shape-based methods and the accuracy of the most successful shape-based methods which are orders of magnitude slower. Volumetric aligned molecular shapes also offer a novel minimum/maximum shape constraint search that allows the user to precisely specify the desired shape and search millions of shapes in a fraction of a second.