Suplementary Material for

Improving drug–target interaction prediction using interaction profiles

Twan van Laarhoven, Sander B. Nabuurs, Elena Marchiori

August 12, 2011

Availability: Extended versions of this material and accompanying implementations are available at http://cs.ru.nl/∼T.vanLaarhoven/drugtarget2011/.

1 Detailed experimental results

Table S1 shows additional results of our experiments with leave-one-out cross-validation.
Table S2 shows the results of our experiments with 10-fold cross-validation.

In addition to the methods described in the main paper, these tables also include results with a correlation kernel, as described by Basilico and Hofmann (2004).

2 Kernel weights

Figure S3 shows the results of our experiments to determine whether the size of the dataset influences the importance of the GIP kernels. These results are discussed in section 4.2 of the main paper.

3 New interactions

Tables S3-S6 show the top 20 predicted putative interactions with our method. Interactions that appear in the ChEMBL database are marked with "[C]", interactions in Drugbank are marked with "[D]", and interactions in Kegg are marked with "[K]". Interactions that appear in any of these databases are marked in bold.

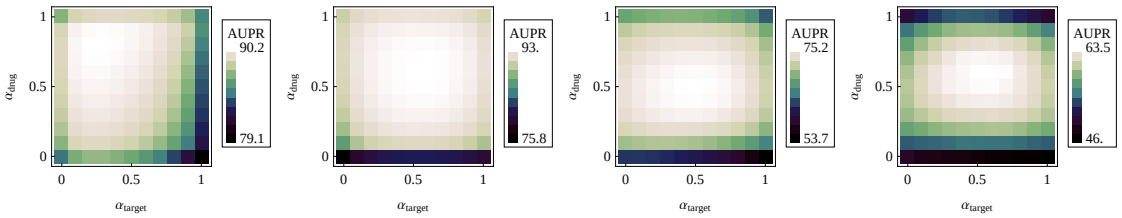
Detailed information about predicted putative interactions and those confirmed by ChEMBL, Drugbank and Kegg can be found at http://cs.ru.nl/∼tvanlaarhoven/drugtarget2011/new-interactions/.

Table S1: Results of leave-one-out cross-validation on the drug target interaction datasets. All scores are normalized to 100. Sensitivity, Specificity and PPV were computed by treating the highest ranked 1% of all pairs as positive.

Dataset	Method	Kernel	AUC	AUPR	Sensitivity	Specificity	PPV
Enzyme	RLS-avg	GIP	98.2	88.1	79.4	99.8	78.7
	RLS-avg	chem/gen	96.6	84.5	81.3	99.8	80.5
	RLS-avg	avg.	97.9	90.5	87.3	99.9	86.5
	RLS-Kron	GIP	98.3*	88.5	79.7	99.8	78.9
	RLS-Kron	chem/gen	96.6	85.6	82.0	99.8	81.2
	RLS-Kron	avg.	97.8	91.5*	88.0*	99.9*	87.1*
	RLS-avg	correlation	97.4	76.5	71.5	99.7	70.9
	RLS-Kron	correlation	95.6	57.4	50.3	99.5	49.8
Ion Channel	RLS-avg	GIP	98.5	91.8	29.0*	100.0*	100.0*
	RLS-avg	chem/gen	97.1	80.7	27.8	100.0	96.0
	RLS-avg	avg.	98.1	93.2	29.0*	100.0*	100.0*
	RLS-Kron	GIP	98.6*	92.7	29.0*	100.0*	100.0*
	RLS-Kron	chem/gen	97.1	77.5	27.8	100.0	95.8
	RLS-Kron	avg.	98.4	94.3*	29.0*	100.0*	100.0*
	RLS-avg	correlation	95.5	81.1	28.8	100.0	99.3
	RLS-Kron	correlation	92.7	64.5	28.0	100.0	96.5
GPCR	RLS-avg	GIP	94.5	70.0	31.5	99.9	94.8
	RLS-avg	chem/gen	94.7	66.0	28.5	99.9	85.8
	RLS-avg	avg.	95.0	77.1	32.9	100.0	99.1
	RLS-Kron	GIP	94.7	71.3	32.0	100.0	96.2
	RLS-Kron	chem/gen	94.8	63.8	26.9	99.8	81.0
	RLS-Kron	avg.	95.4*	79.0*	33.1*	100.0*	99.5*
	RLS-avg	correlation	92.8	56.8	26.3	99.8	79.1
	RLS-Kron	correlation	89.0	45.1	22.4	99.7	67.3
Nuclear Receptor	RLS-avg	GIP	88.7	60.4	14.4	99.9	92.9
	RLS-avg	chem/gen	86.4	54.7	11.1	99.7	71.4
	RLS-avg	avg.	92.5*	67.0	14.4	99.9	92.9
	RLS-Kron	GIP	90.6	61.0	14.4	99.9	92.9
	RLS-Kron	chem/gen	85.9	51.1	10.0	99.6	64.3
	RLS-Kron	avg.	92.2	68.4*	15.6*	100.0*	100.0*
	RLS-avg	correlation	88.6	46.4	14.4	99.9	92.9
	RLS-Kron	correlation	85.2	36.7	12.2	99.8	78.6

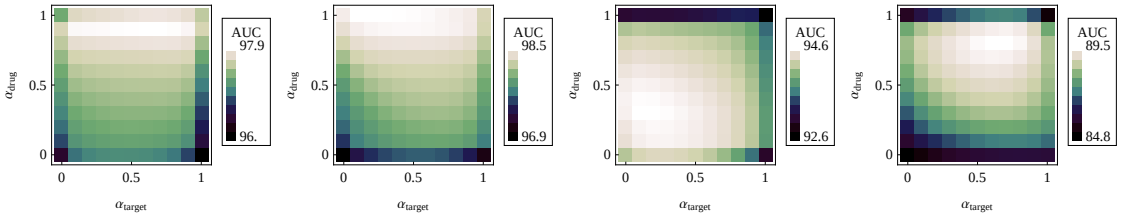
Table S2: Results of 10-fold cross-validation on the drug target interaction datasets. All scores are normalized to 100. Numbers in parentheses give the standard deviation across the 5 repetitions of each experiment. Sensitivity, Specificity and PPV were computed by treating the highest ranked 1% of all pairs as positive.

Dataset	Method	Kernel	AUC	AUPR	Sensitivity	Specificity	PPV
Enzyme	RLS-avg	GIP	97.9 (0.1)*	84.6 (0.2)	77.4 (0.3)	99.76 (0.00)	76.6 (0.3)
	RLS-avg	chem/gen	96.3 (0.1)	83.3 (0.09)	80.4 (0.2)	99.79 (0.00)	79.6 (0.2)
	RLS-avg	avg.	97.4 (0.1)	88.2 (0.2)	84.9 (0.4)	99.84 (0.00)	84.1 (0.4)
	RLS-Kron	GIP	97.5 (0.1)	85.0 (0.2)	77.5 (0.3)	99.77 (0.00)	76.8 (0.3)
	RLS-Kron	chem/gen	96.3 (0.1)	84.5 (0.09)	81.4 (0.4)	99.80 (0.00)	80.6 (0.4)
	RLS-Kron	avg.	97.5 (0.1)	89.6 (0.1)*	86.8 (0.2)*	99.86 (0.00)*	85.9 (0.2)*
	RLS-avg	correlation	96.6 (0.1)	74.0 (0.2)	70.1 (0.4)	99.7 (0.00)	69.4 (0.4)
	RLS-Kron	correlation	94.8 (0.08)	57.0 (0.2)	52.4 (0.2)	99.5 (0.00)	51.9 (0.2)
Ion Channel	RLS-avg	GIP	98.1 (0.1)	88.9 (0.3)	28.9 (0.05)	100.0 (0.00)*	99.77 (0.2)
	RLS-avg	chem/gen	96.8 (0.10)	79.0 (0.3)	27.6 (0.1)	99.95 (0.01)	95.0 (0.4)
	RLS-avg	avg.	97.8 (0.1)	91.3 (0.2)	28.9 (0.03)*	100.0 (0.00)*	99.81 (0.10)*
	RLS-Kron	GIP	98.2 (0.10)*	90.2 (0.3)	28.9 (0.03)*	100.0 (0.00)*	99.81 (0.10)*
	RLS-Kron	chem/gen	96.9 (0.1)	75.8 (0.3)	27.0 (0.3)	99.93 (0.01)	93.1 (1.0)
	RLS-Kron	avg.	98.1 (0.09)	93.0 (0.1)*	28.9 (0.03)*	100.0 (0.00)*	99.81 (0.10)*
	RLS-avg	correlation	94.8 (0.3)	79.6 (0.7)	28.8 (0.03)	99.99 (0.00)	99.4 (0.10)
	RLS-Kron	correlation	92.4 (0.3)	63.7 (0.3)	27.8 (0.2)	99.96 (0.01)	95.8 (0.7)
GPCR	RLS-avg	GIP	93.3 (0.3)	62.2 (1.4)	29.1 (0.8)	99.87 (0.02)	87.6 (2.3)
	RLS-avg	chem/gen	94.2 (0.4)	63.9 (1.1)	27.5 (0.6)	99.82 (0.02)	82.8 (1.8)
	RLS-avg	avg.	94.1 (0.4)	73.3 (1.1)	31.7 (0.4)	99.95 (0.01)	95.4 (1.3)
	RLS-Kron	GIP	92.6 (0.4)	63.2 (1.4)	29.4 (0.7)	99.88 (0.02)	88.4 (2.0)
	RLS-Kron	chem/gen	94.2 (0.3)	61.7 (1.1)	26.0 (0.9)	99.78 (0.03)	78.3 (2.7)
	RLS-Kron	avg.	94.5 (0.4)*	75.1 (1.1)*	31.9 (0.4)*	99.96 (0.01)*	96.1 (1.2)*
	RLS-avg	correlation	91.7 (0.1)	54.3 (0.8)	25.9 (0.7)	99.77 (0.02)	78.0 (2.2)
	RLS-Kron	correlation	88.4 (0.2)	43.8 (0.6)	22.8 (0.6)	99.7 (0.02)	68.5 (1.8)
Nuclear Receptor	RLS-avg	GIP	85.0 (1.8)	48.1 (1.6)	13.8 (0.6)	99.88 (0.04)	88.6 (3.9)
	RLS-avg	chem/gen	85.3 (1.9)	52.4 (1.7)	12.0 (0.5)	99.76 (0.03)	77.1 (3.2)
	RLS-avg	avg.	89.1 (2.2)*	61.8 (1.1)	13.8 (1.0)	99.88 (0.07)	88.6 (6.4)
	RLS-Kron	GIP	85.1 (1.7)	49.1 (1.7)	13.8 (0.6)	99.88 (0.04)	88.6 (3.9)
	RLS-Kron	chem/gen	84.8 (2.1)	48.8 (1.3)	10.2 (0.5)	99.6 (0.03)	65.7 (3.2)
	RLS-Kron	avg.	88.9 (2.5)	63.3 (1.1)*	14.9 (0.6)*	99.95 (0.04)*	95.7 (3.9)*
	RLS-avg	correlation	87.3 (1.1)	41.9 (1.5)	12.7 (1.0)	99.80 (0.07)	81.4 (6.4)
	RLS-Kron	correlation	83.9 (1.0)	34.9 (1.0)	12.4 (0.9)	99.79 (0.06)	80.0 (6.0)



(a) Enzyme (b) Ion Channel (c) GPCR (d) Nuclear Receptor

Figure S1: AUPR scores with different weightings of the kernels. Lighter colors are better. For all datasets $\alpha_{\text{d}} = \alpha_{\text{t}} = 0.5$ gives near optimal results.



(a) Enzyme (b) Ion Channel (c) GPCR (d) Nuclear Receptor

Figure S2: AUC scores with different weightings of the kernels. Lighter colors correspond to higher AUPR values.

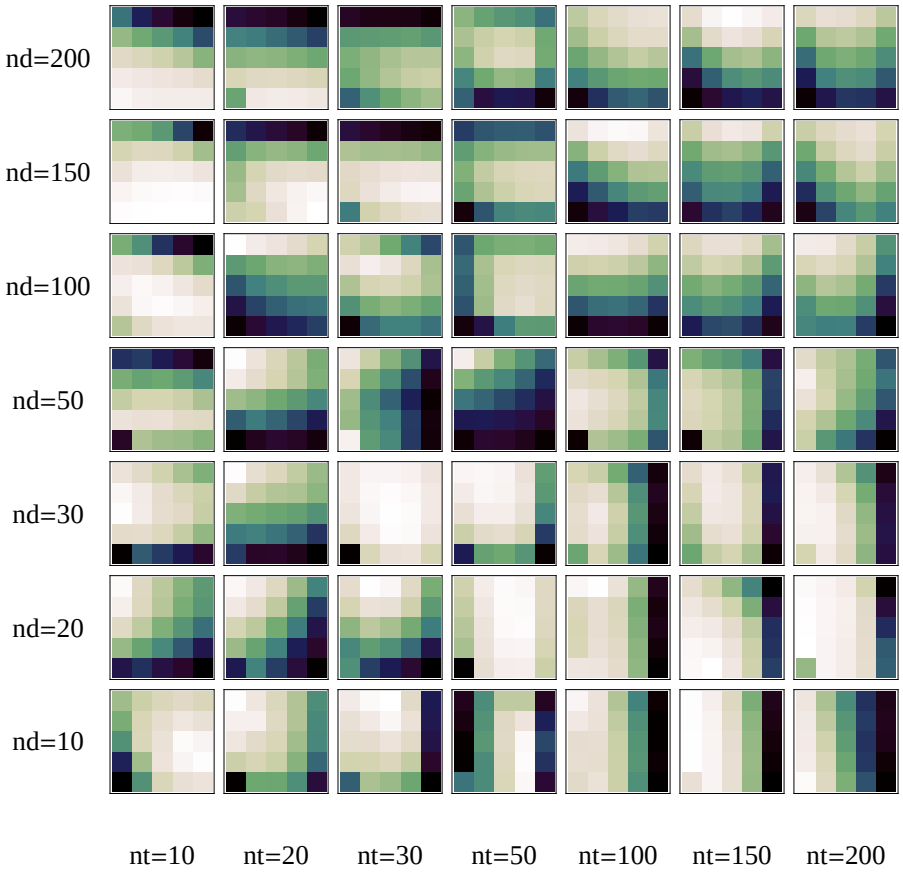


Figure S3: AUC scores for different sized subsets of the Ion Channel dataset, and different weights of the kernel. In each plot α_t increases from left to right, and α_d increases from bottom to top. Lighter colors are better, but note that the scales of each plot are different. The top-right plot corresponds most closely to figure S2b.

Table S3: New interactions predicted in the Enzyme dataset. Interactions that appear in the ChEMBL database are marked with "[C]", interactions in Drugbank are marked with "[D]", and interactions in Kegg are marked with "[K]".

Rank	Score	Pair	Description	NN
1	**0.658**	**D00574**	**Aminoglutethimide**	0.296
[C]		**hsa1589**	**CYP21A2: cytochrome P450,**	
			family 21, subfamily A, polypeptide 2 (EC:1.14.99.10)	0.255
2	**0.572**	**D00542**	**Halothane**	0.667
[D]		**hsa1571**	**CYP2E1: cytochrome P450, family 2,**	
			subfamily E, polypeptide 1 (EC:1.14.14.1)	0.607
3	**0.558**	**D00139**	**Methoxsalen**	0.310
[D]		**hsa1543**	**CYP1A1: cytochrome P450, family 1,**	
			subfamily A, polypeptide 1 (EC:1.14.14.1)	0.735
4	0.538	D00437	Nifedipine	0.237
		hsa1585	CYP11B2: cytochrome P450,	
			family 11, subfamily B, polypeptide 2 (EC:1.14.15.4 1.14.15.5)	0.930
5	**0.526**	**D00437**	**Nifedipine**	0.237
[D]		**hsa1559**	**CYP2C9: cytochrome P450, family 2,**	
			subfamily C, polypeptide 9 (EC:1.14.13.48 1.14.13.49 1.14.13.80)	0.924
6	0.508	D00528	Caffeine	0.250
		hsa1549	CYP2A7: cytochrome P450, family 2,	
			subfamily A, polypeptide 7 (EC:1.14.14.1)	0.944
7	0.496	D00691	Dyphylline	0.684
		hsa5152	PDE9A: phosphodiesterase 9A (EC:3.1.4.35)	0.171
8	0.472	D00410	Metyrapone	0.345
		hsa1583	CYP11A1: cytochrome P450,	
			family 11, subfamily A, polypeptide 1 (EC:1.14.15.6)	0.335
9	0.456	D03670	Deferoxamine	0.140
		hsa1579	CYP4A11: cytochrome P450,	
			family 4, subfamily A, polypeptide 11 (EC:1.14.15.3)	0.947
10	0.437	D00691	Dyphylline	0.684
		hsa8654	PDE5A: phosphodiesterase 5A, cGMP-specific (EC:3.1.4.35)	0.217
11	0.423	D00126	Ibuprofen	0.524
		hsa247	ALOX15B: arachidonate 15-lipoxygenase, type B (EC:1.13.11.33)	0.468
12	0.416	D00410	Metyrapone	0.345
		hsa1543	CYP1A1: cytochrome P450, family 1,	
			subfamily A, polypeptide 1 (EC:1.14.14.1)	0.735
13	**0.408**	**D00449**	**Sulfinpyrazone**	0.677
[C]		**hsa5742**	**PTGS1: prostaglandin-endoperoxide**	
			synthase 1 (prostaglandin G/H synthase and cyclooxygenase) (EC:1.14.99.1)	0.640
14	**0.400**	**D05458**	**Phentermine**	0.562
[D]		**hsa4128**	**MAOA**	0.748
15	**0.397**	**D00947**	**Linezolid**	0.500
[C]		**hsa4129**	**MAOB: monoamine oxidase B (EC:1.4.3.4)**	0.748
16	**0.396**	**D00410**	**Metyrapone**	0.345
[D]		**hsa1585**	**CYP11B2: cytochrome P450,**	
			family 11, subfamily B, polypeptide 2 (EC:1.14.15.4 1.14.15.5)	0.930
17	0.380	D00126	Ibuprofen	0.524
		hsa246	ALOX15: arachidonate 15-lipoxygenase (EC:1.13.11.33)	0.668
18	**0.340**	**D00691**	**Dyphylline**	0.632
[D]		**hsa5150**	**PDE7A: phosphodiesterase 7A (EC:3.1.4.17)**	0.600
19	**0.330**	**D00537**	**Topiramate**	0.265
[C]		**hsa759**	**CA1: carbonic anhydrase I (EC:4.2.1.1)**	0.602
20	**0.330**	**D00097**	**Salicylic acid**	0.750
[D]		**hsa5743**	**PTGS2: prostaglandin-endoperoxide**	
			synthase 2 (prostaglandin G/H synthase and cyclooxygenase) (EC:1.14.99.1)	0.640

Table S4: New interactions predicted in the Ion Channel dataset. Interactions that appear in the ChEMBL database are marked with "[C]", interactions in Drugbank are marked with "[D]", and interactions in Kegg are marked with "[K]".

Rank	Score	Pair	Description	NN
1	**0.510**	**D00438**	**Nimodipine**	0.750
[D,K]		**hsa779**	**CACNA1S: calcium channel,**	
			voltage-dependent, L type, alpha 1S subunit	0.578
2	0.475	D00726	Metoclopramide	0.200
		hsa1138	CHRNA5: cholinergic receptor, nicotinic, alpha 5	0.443
3	**0.459**	**D03365**	**Nicotine**	0.409
[C,D]		**hsa1137**	**CHRNA4: cholinergic receptor, nicotinic, alpha 4**	0.528
4	0.399	D02098	Proparacaine hydrochloride	0.667
		hsa8645	KCNK5: potassium channel, subfamily K, member 5	0.013
5	**0.385**	**D00552**	**Benzocaine**	0.579
[K]		**hsa6331**	**SCN5A: sodium channel, voltage-gated, type V, alpha subunit**	0.604
6	0.383	D00775	Riluzole	0.000
		hsa2898	GRIK2: glutamate receptor, ionotropic, kainate 2	0.811
7	0.382	D00294	Diazoxide	0.175
		hsa10060	ABCC9: ATP-binding cassette, sub-family C (CFTR/MRP), member 9	0.682
8	0.367	D00477	Procainamide hydrochloride	0.714
		hsa6336	SCN10A: sodium channel, voltage-gated, type X, alpha subunit	0.604
9	0.349	D00640	Propafenone hydrochloride	0.457
		hsa6336	SCN10A: sodium channel, voltage-gated, type X, alpha subunit	0.604
10	0.336	D00524	Carbachol	0.350
		hsa1134	CHRNA1: cholinergic receptor, nicotinic, alpha 1 (muscle)	0.460
11	**0.326**	**D00538**	**Zonisamide**	0.364
[D,K]		**hsa6331**	**SCN5A: sodium channel, voltage-gated, type V, alpha subunit**	0.604
12	**0.319**	**D01969**	**Gallopamil hydrochloride**	0.865
[K]		**hsa778**	**CACNA1F: calcium channel,**	
			voltage-dependent, L type, alpha 1F subunit	0.561
13	0.318	D00547	Sevoflurane	0.042
		hsa2570	GABRR2	0.683
14	0.313	D00349	Isradipine	0.733
		hsa773	CACNA1A: calcium channel,	
			voltage-dependent, P/Q type, alpha 1A subunit	0.285
15	0.313	D00524	Carbachol	0.350
		hsa1139	CHRNA7: cholinergic receptor, nicotinic, alpha 7	0.356
16	**0.307**	**D03830**	**Diltiazem malate**	0.358
[K]		**hsa776**	**CACNA1D: calcium channel,**	
			voltage-dependent, L type, alpha 1D subunit	0.641
17	0.301	D00799	Trifluoperazine hydrochloride	0.879
		hsa3782	KCNN3: potassium intermediate/small	
			conductance calcium-activated channel, subfamily N, member 3	0.630
18	**0.292**	**D00616**	**Diltiazem hydrochloride**	0.404
[K]		**hsa776**	**CACNA1D: calcium channel,**	
			voltage-dependent, L type, alpha 1D subunit	0.641
19	0.287	D00136	Haloperidol	0.303
		hsa116443	GRIN3A: glutamate receptor, ionotropic, N-methyl-D-aspartate 3A	0.443
20	**0.284**	**D00283**	**Clozapine**	0.371
[C]		**hsa170572**	**HTR3C**	0.738

Table S5: New interactions predicted in the GPCR dataset. Interactions that appear in the ChEMBL database are marked with "[C]", interactions in Drugbank are marked with "[D]", and interactions in Kegg are marked with "[K]".

Rank	Score	Pair	Description	NN
1	**0.392**	**D00283**	**Clozapine**	0.769
[C,D]		**hsa1814**	**DRD3: dopamine receptor D3**	0.455
2	**0.300**	**D02358**	**Metoprolol**	0.750
[C,D]		**hsa154**	**ADRB2: beta-2 adrenergic receptor**	0.434
3	0.299	D00604	Clonidine hydrochloride	0.933
		hsa147	ADRA1B: alpha-1B adrenergic receptor	0.435
4	0.294	D03966	Eglumegad	0.036
		hsa2914	GRM4: glutamate receptor, metabotropic 4	0.768
5	0.292	D00255	Carvedilol	0.380
		hsa152	ADRA2C: alpha-2C adrenergic receptor	0.489
6	**0.291**	**D04625**	**Isoetharine**	0.737
[K]		**hsa154**	**ADRB2: beta-2 adrenergic receptor**	0.434
7	0.289	D03966	Eglumegad	0.036
		hsa2917	GRM7: glutamate receptor, metabotropic 7	0.758
8	**0.288**	**D02340**	**Loxapine**	0.769
[D]		**hsa1812**	**DRD1: dopamine receptor D1**	0.205
9	0.288	D00503	Perphenazine	0.857
		hsa1816	DRD5: dopamine receptor D5	0.529
10	0.270	D00682	Carboprost tromethamine	0.914
		hsa5739	PTGIR: prostaglandin I2 receptor (IP)	0.150
11	0.268	D01973	Eletriptan hydrobromide	0.417
		hsa3361	HTR5A: 5-hydroxytryptamine (serotonin) receptor 5A	0.304
12	**0.262**	**D00790**	**Chlorprothixene**	0.826
[D]		**hsa1814**	**DRD3: dopamine receptor D3**	0.455
13	0.260	D00503	Perphenazine	0.857
		hsa3356	HTR2A: 5-hydroxytryptamine (serotonin) receptor 2A	0.186
14	**0.260**	**D00079**	**Dinoprostone**	0.852
[C,D]		**hsa5731**	**PTGER1: prostaglandin E receptor 1 (subtype EP1), 42kDa**	0.150
15	0.257	D02884	Ambuphylline	0.650
		hsa140	ADORA3: adenosine A3 receptor	0.477
16	**0.256**	**D02250**	**Octreotide acetate**	0.759
[K]		**hsa6751**	**SSTR1: somatostatin receptor 1**	0.456
17	0.251	D02354	Thiethylperazine	0.793
		hsa1814	DRD3: dopamine receptor D3	0.455
18	**0.250**	**D05113**	**Naltrexone**	0.714
[C,D]		**hsa4986**	**OPRK1: opioid receptor, kappa 1**	0.563
19	0.248	D01712	Theophylline sodium acetate	0.684
		hsa140	ADORA3: adenosine A3 receptor	0.477
20	**0.246**	**D00095**	**Epinephrine**	0.929
[C,K]		**hsa155**	**ADRB3: beta-3 adrenergic receptor**	0.423

Table S6: New interactions predicted in the Nuclear Receptor dataset. Interactions that appear in the ChEMBL database are marked with "[C]", interactions in Drugbank are marked with "[D]", and interactions in Kegg are marked with "[K]".

Rank	Score	Pair	Description	NN
1	0.307	D00316	Etretinate	0.371
		hsa6096	RORB: RAR-related orphan receptor B	0.179
2	0.221	D00182	Norethindrone	0.875
		hsa2099	ESR1: estrogen receptor 1	0.130
3	0.212	D00348	Isotretinoin	1.000
		hsa5915	RARB: retinoic acid receptor, beta	0.729
4	0.204	D01132	Tazarotene	0.146
		hsa6097	RORC: RAR-related orphan receptor C	0.458
5	0.203	D00348	Isotretinoin	1.000
		hsa5916	RARG: retinoic acid receptor, gamma	0.694
6	**0.175**	**D00898**	**Dienestrol**	0.818
[K]		**hsa2100**	**ESR2: estrogen receptor 2 (ER beta)**	0.385
7	**0.166**	**D00075**	**Testosterone**	0.833
[C]		**hsa5241**	**PGR: progesterone receptor**	0.255
8	**0.162**	**D00554**	**Ethinyl estradiol**	0.826
[C,K]		**hsa2100**	**ESR2: estrogen receptor 2 (ER beta)**	0.385
9	0.156	D01132	Tazarotene	0.146
		hsa190	NR0B1: nuclear receptor subfamily 0, group B, member 1	0.071
10	0.149	D00327	Fluoxymesterone	0.621
		hsa5241	PGR: progesterone receptor	0.255
11	**0.147**	**D00067**	**Estrone**	0.818
[C,K]		**hsa2100**	**ESR2: estrogen receptor 2 (ER beta)**	0.385
12	**0.139**	**D00690**	**Mometasone furoate**	0.614
[D,K]		**hsa2908**	**NR3C1: nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)**	0.257
13	0.136	D00348	Isotretinoin	1.000
		hsa6258	RXRG: retinoid X receptor, gamma	0.053
14	**0.136**	**D00088**	**Hydrocortisone**	0.690
[C]		**hsa5241**	**PGR: progesterone receptor**	0.257
15	**0.133**	**D00443**	**Spironolactone**	0.677
[C]		**hsa5241**	**PGR: progesterone receptor**	0.231
16	0.132	D00348	Isotretinoin	1.000
		hsa6256	RXRA: retinoid X receptor, alpha	0.233
17	0.132	D00348	Isotretinoin	1.000
		hsa6257	RXRB: retinoid X receptor, beta	0.211
18	0.129	D00094	Tretinoin	0.190
		hsa6095	RORA: RAR-related orphan receptor A	0.578
19	**0.125**	**D00585**	**Mifepristone**	0.514
[C]		**hsa2099**	**ESR1: estrogen receptor 1**	0.131
20	**0.122**	**D00075**	**Testosterone**	0.833
[C]		**hsa2099**	**ESR1: estrogen receptor 1**	0.119

4 Comparing new interactions with Bleakley & Yamanishi

Tables S7-S10 show a comparison between new interactions predicted by our method, and those predicted by Bleakley and Yamanishi (2009). We compare the 50 highest ranked interactions, and of those we show only those that are found in the ChemblDb, DrugBank or KEGG databases.

Table S7: Comparing the 50 highest ranked predictions for the Enzyme dataset.

Interactions found by both methods

D00574	Aminoglutethimide	hsa1589	CYP21A2: cytochrome P450, family 21, subfamily A, polypeptide 2 (EC:1.14.99.10)
D00542	Halothane	hsa1571	CYP2E1: cytochrome P450, family 2, subfamily E, polypeptide 1 (EC:1.14.14.1)
D00139	Methoxsalen	hsa1543	CYP1A1: cytochrome P450, family 1, subfamily A, polypeptide 1 (EC:1.14.14.1)
D00437	Nifedipine	hsa1559	CYP2C9: cytochrome P450, family 2, subfamily C, polypeptide 9 (EC:1.14.13.48 1.14.13.49 1.14.13.80)
D00947	Linezolid	hsa4129	MAOB: monoamine oxidase B (EC:1.4.3.4)
D00410	Metyrapone	hsa1585	CYP11B2: cytochrome P450, family 11, subfamily B, polypeptide 2 (EC:1.14.15.4 1.14.15.5)
D00691	Dyphylline	hsa5150	PDE7A: phosphodiesterase 7A (EC:3.1.4.17)
D00097	Salicylic acid	hsa5743	PTGS2: prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) (EC:1.14.99.1)
D02441	Ethoxzolamide	hsa760	CA2: carbonic anhydrase II (EC:4.2.1.1)
D03365	Nicotine	hsa1548	CYP2A6: cytochrome P450, family 2, subfamily A, polypeptide 6 (EC:1.14.14.1)

Interactions only found by our method

D00449	Sulfinpyrazone	hsa5742	PTGS1: prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) (EC:1.14.99.1)
D05458	Phentermine	hsa4128	MAOA
D00537	Topiramate	hsa759	CA1: carbonic anhydrase I (EC:4.2.1.1)
D00401	Methimazole	hsa4025	LPO: lactoperoxidase (EC:1.11.1.7)
D00454	Olanzapine	hsa1576	CYP3A4: cytochrome P450, family 3, subfamily A, polypeptide 4 (EC:1.14.13.67 1.14.13.97 1.14.13.32)

Interactions only found by Bleakley & Yamanishi

D00448	Sulfasalazine	hsa5743	PTGS2: prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) (EC:1.14.99.1)
D00448	Sulfasalazine	hsa5742	PTGS1: prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) (EC:1.14.99.1)
D02441	Ethoxzolamide	hsa762	CA4: carbonic anhydrase IV (EC:4.2.1.1)
D00560	Pimozide	hsa1576	CYP3A4: cytochrome P450, family 3, subfamily A, polypeptide 4 (EC:1.14.13.67 1.14.13.97 1.14.13.32)
D00300	Diphenhydramine	hsa5742	PTGS1: prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) (EC:1.14.99.1)

Table S8: Comparing the 50 highest ranked predictions for the Ion Channel dataset.

Interactions found by both methods

D00438	Nimodipine	hsa779	CACNA1S: calcium channel, voltage-dependent, L type, alpha 1S subunit

Interactions only found by our method

D03365	Nicotine	hsa1137	CHRNA4: cholinergic receptor, nicotinic, alpha 4
D00552	Benzocaine	hsa6331	SCN5A: sodium channel, voltage-gated, type V, alpha subunit
D00538	Zonisamide	hsa6331	SCN5A: sodium channel, voltage-gated, type V, alpha subunit
D01969	Gallopamil hydrochloride	hsa778	CACNA1F: calcium channel, voltage-dependent, L type, alpha 1F subunit
D03830	Diltiazem malate	hsa776	CACNA1D: calcium channel, voltage-dependent, L type, alpha 1D subunit
D00616	Diltiazem hydrochloride	hsa776	CACNA1D: calcium channel, voltage-dependent, L type, alpha 1D subunit
D00283	Clozapine	hsa170572	HTR3C
D00451	Sumatriptan	hsa170572	HTR3C
D00619	Verapamil hydrochloride	hsa778	CACNA1F: calcium channel, voltage-dependent, L type, alpha 1F subunit
D03365	Nicotine	hsa1134	CHRNA1: cholinergic receptor, nicotinic, alpha 1 (muscle)
D03365	Nicotine	hsa1139	CHRNA7: cholinergic receptor, nicotinic, alpha 7

Interactions only found by Bleakley & Yamanishi

D06172	Tocainide	hsa6323	SCN1A: sodium channel, voltage-gated, type I, alpha subunit
D06172	Tocainide	hsa6328	SCN3A: sodium channel, voltage-gated, type III, alpha subunit
D06172	Tocainide	hsa6329	SCN4A: sodium channel, voltage-gated, type IV, alpha subunit
D00553	Prilocaine	hsa6328	SCN3A: sodium channel, voltage-gated, type III, alpha subunit
D06172	Tocainide	hsa6326	SCN2A: sodium channel, voltage-gated, type II, alpha subunit
D06172	Tocainide	hsa6334	SCN8A: sodium channel, voltage gated, type VIII, alpha subunit
D06172	Tocainide	hsa6335	SCN9A: sodium channel, voltage-gated, type IX, alpha subunit
D00553	Prilocaine	hsa6323	SCN1A: sodium channel, voltage-gated, type I, alpha subunit
D00553	Prilocaine	hsa6326	SCN2A: sodium channel, voltage-gated, type II, alpha subunit
D00553	Prilocaine	hsa6334	SCN8A: sodium channel, voltage gated, type VIII, alpha subunit
D00553	Prilocaine	hsa6336	SCN10A: sodium channel, voltage-gated, type X, alpha subunit
D00294	Diazoxide	hsa3767	KCNJ11: potassium inwardly-rectifying channel, subfamily J, member 11
D00319	Felodipine	hsa783	CACNB2: calcium channel, voltage-dependent, beta 2 subunit

Table S9: Comparing the 50 highest ranked predictions for the GPCR dataset.

Interactions found by both methods

D00283	Clozapine	hsa1814	DRD3: dopamine receptor D3
D02358	Metoprolol	hsa154	ADRB2: beta-2 adrenergic receptor
D04625	Isoetharine	hsa154	ADRB2: beta-2 adrenergic receptor
D00095	Epinephrine	hsa155	ADRB3: beta-3 adrenergic receptor
D02147	Albuterol	hsa153	ADRB1: beta-1 adrenergic receptor
D00283	Clozapine	hsa1132	CHRM4: cholinergic receptor, muscarinic 4
D04375	Guanabenz	hsa151	ADRA2B: alpha-2B adrenergic receptor
D00283	Clozapine	hsa152	ADRA2C: alpha-2C adrenergic receptor
D00283	Clozapine	hsa1131	CHRM3: cholinergic receptor, muscarinic 3
D00371	Theophylline	hsa135	ADORA2A: adenosine A2a receptor
D00283	Clozapine	hsa11255	HRH3: histamine receptor H3
D00454	Olanzapine	hsa152	ADRA2C: alpha-2C adrenergic receptor
D00715	Hyoscine methobromide	hsa1129	CHRM2: cholinergic receptor, muscarinic 2
D00283	Clozapine	hsa1133	CHRM5: cholinergic receptor, muscarinic 5

Interactions only found by our method

D02340	Loxapine	hsa1812	DRD1: dopamine receptor D1
D00790	Chlorprothixene	hsa1814	DRD3: dopamine receptor D3
D00079	Dinoprostone	hsa5731	PTGER1: prostaglandin E receptor 1 (subtype EP1), 42kDa
D02250	Octreotide acetate	hsa6751	SSTR1: somatostatin receptor 1
D05113	Naltrexone	hsa4986	OPRK1: opioid receptor, kappa 1
D00397	Tropicamide	hsa1131	CHRM3: cholinergic receptor, muscarinic 3
D00442	Octreotide	hsa6755	SSTR5: somatostatin receptor 5
D00397	Tropicamide	hsa1133	CHRM5: cholinergic receptor, muscarinic 5
D00514	Dexmedetomidine	hsa151	ADRA2B: alpha-2B adrenergic receptor
D00442	Octreotide	hsa6753	SSTR3
D02356	Verapamil	hsa152	ADRA2C: alpha-2C adrenergic receptor
D02349	Dipivefrin	hsa151	ADRA2B: alpha-2B adrenergic receptor
D00136	Haloperidol	hsa152	ADRA2C: alpha-2C adrenergic receptor
D01712	Theophylline sodium acetate	hsa136	ADORA2B: adenosine A2b receptor

Interactions only found by Bleakley & Yamanishi

D02349	Dipivefrin	hsa154	ADRB2: beta-2 adrenergic receptor
D00454	Olanzapine	hsa3357	HTR2B: 5-hydroxytryptamine (serotonin) receptor 2B
D00371	Theophylline	hsa134	ADORA1: adenosine A1 receptor
D00110	Cocaine	hsa1128	CHRM1: cholinergic receptor, muscarinic 1
D00106	Epoprostenol	hsa5739	PTGIR: prostaglandin I2 receptor (IP)
D00454	Olanzapine	hsa3350	HTR1A: 5-hydroxytryptamine (serotonin) receptor 1A
D00394	Trimipramine	hsa3269	HRH1: histamine receptor H1
D04375	Guanabenz	hsa152	ADRA2C: alpha-2C adrenergic receptor

Table S10: Comparing the 50 highest ranked predictions for the Nuclear Receptor dataset.

Interactions found by both methods

D00898	Dienestrol	hsa2100	ESR2: estrogen receptor 2 (ER beta)
D00075	Testosterone	hsa5241	PGR: progesterone receptor
D00554	Ethinyl estradiol	hsa2100	ESR2: estrogen receptor 2 (ER beta)
D00067	Estrone	hsa2100	ESR2: estrogen receptor 2 (ER beta)
D00690	Mometasone furoate	hsa2908	NR3C1: nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)
D00088	Hydrocortisone	hsa5241	PGR: progesterone receptor
D00443	Spironolactone	hsa5241	PGR: progesterone receptor
D00585	Mifepristone	hsa2099	ESR1: estrogen receptor 1
D00075	Testosterone	hsa2099	ESR1: estrogen receptor 1
D00327	Fluoxymesterone	hsa2908	NR3C1: nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)
D00627	Telmisartan	hsa5465	PPARA: peroxisome proliferator-activated receptor alpha
D00565	Fenofibrate	hsa5468	PPARG: peroxisome proliferator-activated receptor gamma
D00279	Clofibrate	hsa5468	PPARG: peroxisome proliferator-activated receptor gamma

Interactions only found by our method

D01115	Eplerenone	hsa2908	NR3C1: nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)
D00312	Estrone sodium sulfate	hsa2100	ESR2: estrogen receptor 2 (ER beta)
D00962	Clomiphene citrate	hsa2100	ESR2: estrogen receptor 2 (ER beta)
D01115	Eplerenone	hsa367	AR: androgen receptor
D01115	Eplerenone	hsa5241	PGR: progesterone receptor
D00443	Spironolactone	hsa2908	NR3C1: nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)
D00951	Medroxyprogesterone acetate	hsa2099	ESR1: estrogen receptor 1

Interactions only found by Bleakley & Yamanishi

D00961	Bicalutamide	hsa2099	ESR1: estrogen receptor 1
D00066	Progesterone	hsa2100	ESR2: estrogen receptor 2 (ER beta)

5 Derivation of RLS-Kron method

This is a more detailed version of the derivation in section 3.5 of the main paper. Let

$$K_\mathrm{d} = V_\mathrm{d}\Lambda_\mathrm{d}{V_\mathrm{d}}^T \text{ and}$$
$$K_\mathrm{t} = V_\mathrm{t}\Lambda_\mathrm{t}V_\mathrm{t}^T$$

be the eigendecompositions of the two kernel matrices.

Then by properties of the Kronecker product $K = K_\mathrm{d} \otimes K_\mathrm{t} = V\Lambda V^T$, where $\Lambda = \Lambda_\mathrm{d} \otimes \Lambda_\mathrm{t}$ and $V = V_\mathrm{d} \otimes V_\mathrm{t}$.

Now

$$\begin{aligned}
&\mathrm{vec}(\hat{Y}^T)\\
=&\{\textit{by definition of RLS-Kron method}\}\\
&(K + \sigma I)^{-1}\mathrm{vec}(Y^T)\\
=&\{K = V\Lambda V^T\text{, see above}\}\\
&V\Lambda V^T(V\Lambda V^T + \sigma I)^{-1}\mathrm{vec}(Y^T)\\
=&\{V \textit{ is orthogonal, so } I = VIV^T\}\\
&V\Lambda V^T(V(\Lambda + \sigma I)V^T)^{-1}\mathrm{vec}(Y^T)\\
=&\{V \textit{ is orthogonal}\}\\
&V\Lambda V^T V(\Lambda + \sigma I)^{-1}V^T\mathrm{vec}(Y^T)\\
=&\{V \textit{ is orthogonal}\}\\
&V\Lambda(\Lambda + \sigma I)^{-1}V^T\mathrm{vec}(Y^T)\\
=&\{V^T = {V_d}^T \otimes {V_t}^T\}\\
&V\Lambda(\Lambda + \sigma I)^{-1}(({V_\mathrm{d}}^T \otimes V_\mathrm{t}^T)\mathrm{vec}(Y^T))\\
=&\{(A \otimes B)vec(X) = vec(BXA^T)\}\\
&V\Lambda(\Lambda + \sigma I)^{-1}\mathrm{vec}(V_\mathrm{t}^T Y^T V_\mathrm{d})\\
=&\{V = V_d \otimes V_t\}\\
&(V_\mathrm{d} \otimes V_\mathrm{t})\Lambda(\Lambda + \sigma I)^{-1}\mathrm{vec}(V_\mathrm{t}^T Y^T V_\mathrm{d})\\
=&\{\textit{Introduce unvec such that } vec(unvec(X)) = X\}\\
&(V_\mathrm{d} \otimes V_\mathrm{t})\mathrm{vec}\big(\mathrm{unvec}\big(\Lambda(\Lambda + \sigma I)^{-1}\mathrm{vec}(V_\mathrm{t}^T Y^T V_\mathrm{d})\big)\big)\\
=&\{(A \otimes B)vec(X) = vec(BXA^T) = vec((AX^TB^T)^T)\}\\
&\mathrm{vec}\big(\big(V_\mathrm{d}\,\mathrm{unvec}(\Lambda(\Lambda + \sigma I)^{-1}\mathrm{vec}(V_\mathrm{t}^T Y^T V_\mathrm{d}))^T\, V_\mathrm{t}^T\big)^T\big)
\end{aligned}$$

To match the paper we can define Z by

$$\mathrm{vec}(Z) = \Lambda(\Lambda + \sigma I)^{-1}\mathrm{vec}(V_\mathrm{t}^T Y^T V_\mathrm{d}).$$

Then

$$\hat{Y} = V_\mathrm{d} Z^T V_\mathrm{t}^T.$$