# Disclosing incoherent sparse and low-rank patterns inside homologous GPCR tasks for better modelling of ligand bioactivities

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**Supporting Tables**

**Table S1.** Description of GPCR datasets

| Group | Dataset | UniProt ID | Gene Name | # of Ligands | Clinical Significance | Homologous Tasks UniProt ID (# of Ligands) | Class/ Subfamily |
|---|---|---|---|---|---|---|---|
| A | A1 | P30939 | HTR1F | 174 | movement disorder[1] | Q13639 (445); P28221 (1326); P34969 (1729) | A / Aminergic receptors |
| | A2 | P28566 | HTR1E | 223 | psychiatric disorder[2] | | |
| | A3 | P47898 | HTR5A | 307 | Schizophrenia[3] | | |
| B | B1 | O95136 | S1PR2 | 270 | Cell proliferation[4] | O95977(438);Q99500(1131);P21453(2651) | A / Lipid receptors |
| | B2 | Q9H228 | S1PR5 | 320 | Huntington's disease[5] | | |
| C | C1 | Q15391 | P2RY14 | 92 | Immune system[6] | P47900(583);Q9H244(1152) | Class A/ Nucleotide receptors |
| | C2 | P51582 | P2RY4 | 154 | K+ secretion1[7] | | |
| | C3 | Q15077 | P2RY6 | 227 | Proliferation of tumour cells [8] | | |
| | C4 | P41231 | P2RY2 | 308 | Migration and invasion of breast cancer [9] | | |
| D | D1 | P30550 | GRPR | 56 | Central nervous systems [10] | P30556 (1049); P46663 (789) | Class A / Peptide receptors |
| | D2 | P28336 | NMBR | 175 | Growth regulation[11] | | |
| | D3 | P32247 | BRS3 | 332 | Metabolic defects and obesity [12] | | |
| E | E1 | P32302 | CXCR5 | 77 | Lymph node metastases,etc [13] | P25106(483);P41597(1520);P51681(2132) | Class A / Protein receptors |
| | E2 | P51685 | CCR8 | 179 | Monocyte chemotaxis and thymic cell apoptosis [14] | | |
| | E3 | P51684 | CCR6 | 264 | Crohn's disease [15] | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | E4 | P51679 | CCR4 | 368 | Cutaneous T-cell lymphoma [16] | | |
| F | F1 | P49019 | HCAR3 | 119 | Inhibition of lipolytic activity [17] | Q8TDS4(500) | Class A / Alicarboxylic acid receptors |
| | F2 | Q9BXC0 | HCAR1 | 150 | Inhibits lipolysis in fat cells [18] | | |
| G | G1 | O95838 | GLP2R | 76 | Enterocyte apoptosis [19] | P47871(865); P30411(717);Q16602(701) | Class B1/ Peptide receptors |
| | G2 | P48546 | GIPR | 95 | Insulin secretion [20] | | |
| H | H1 | Q14831 | GRM7 | 52 | Hearing Loss and Deafness[21] | Q13255(802); P41594(2044) | Class C / Amino acid receptors |
| | H2 | O00222 | GRM8 | 65 | Addiction vulnerability [22] | | |
| | H3 | O15303 | GRM6 | 73 | Schizophrenia [23] | | |
| | H4 | Q14832 | GRM3 | 122 | Schizophrenia[24] | | |
| I | I1 | Q96LB2 | MRGPRX1 | 74 | Neurodermatitis[25] | None | Class A/ Orphan receptors |
| | I2 | Q9UPC5 | GPR34 | 94 | immunological diseases and cancer[26] | | |
| | I3 | Q7Z601 | GPR142 | 95 | Fusariosis[27] | | |
| | I4 | P32249 | GPR183 | 102 | β -cell dysfunction[28] | | |
| | I5 | Q9GZN0 | GPR88 | 190 | chorea, speech delay, and learning disabilities[29] | | |
| | I6 | Q9HC97 | GPR35 | 330 | inflammatory bowel disease[30] | | |
| | I7 | Q9NQS5 | GPR84 | 360 | non-alcoholic fatty liver disease [31] | | |

**Table S2.** Comparison on top 100 selected features with other feature learning methods

| Group | Dataset | $r^2$ (↑) | | | | | | | RMSE(↓) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PCC | Lasso | RR | MTLa | cFSGL | MTR-GL | MTR-ISLR | PCC | Lasso | RR | MTLa | cFSGL | MTR-GL | MTR-ISLR |
| A | A1 | 0.3424 | 0.2736 | 0.2661 | 0.3526 | 0.2983 | 0.3587 | **0.3821** | 0.7283 | 0.7496 | 0.8197 | 0.7642 | 0.7925 | 0.7571 | **0.7194** |
| | A2 | 0.5981 | 0.6208 | 0.6382 | 0.6338 | 0.61 | 0.6628 | **0.6754** | 0.6402 | 0.6314 | 0.6457 | 0.6113 | 0.6305 | 0.6221 | **0.6045** |
| | A3 | 0.4281 | 0.5119 | 0.5265 | 0.5462 | 0.4671 | 0.5662 | **0.5896** | 0.7929 | 0.7288 | 0.7585 | 0.7694 | 0.7609 | 0.7593 | **0.7232** |
| B | B1 | 0.7112 | 0.7444 | 0.7541 | 0.7601 | 0.6585 | 0.7564 | **0.7857** | 0.7064 | 0.6977 | 0.6721 | 0.6984 | 0.7143 | 0.6852 | **0.6648** |
| | B2 | 0.466 | **0.6265** | 0.5639 | 0.6248 | 0.5408 | 0.5964 | 0.6154 | 0.6775 | **0.5514** | 0.5582 | 0.554 | 0.6285 | 0.5735 | 0.5717 |
| C | C1 | 0.6219 | 0.6773 | 0.6807 | 0.6714 | 0.6716 | 0.6947 | **0.7025** | 0.9793 | **0.8673** | 0.9067 | 0.8874 | 0.8886 | 0.9079 | 1.0861 |
| | C2 | 0.5158 | 0.5608 | 0.5175 | **0.5616** | 0.5382 | 0.5284 | 0.5469 | 0.631 | 0.6195 | 0.6242 | **0.575** | 0.613 | 0.6364 | 0.6379 |
| | C3 | 0.4759 | 0.5383 | 0.5157 | 0.5402 | 0.3296 | 0.5704 | **0.5796** | 0.6752 | 0.6644 | 0.66 | 0.7284 | 0.7645 | 0.6636 | **0.6509** |
| | C4 | 0.494 | 0.5477 | 0.5783 | 0.571 | 0.6053 | 0.5844 | **0.6352** | 0.6958 | 0.6507 | **0.6209** | 0.6801 | 0.6213 | 0.6616 | 0.6435 |
| D | D1 | 0.6647 | 0.7296 | 0.7219 | 0.7563 | 0.7723 | **0.7808** | 0.6952 | 1.0938 | 0.9523 | 0.9756 | 0.9963 | 0.8195 | **0.815** | 0.9179 |
| | D2 | 0.4546 | 0.5183 | 0.5368 | 0.5291 | 0.5649 | 0.5607 | **0.5732** | 0.6885 | 0.6244 | 0.5865 | 0.583 | 0.5742 | 0.5933 | **0.5735** |
| | D3 | 0.5071 | 0.5046 | 0.5035 | 0.505 | 0.5079 | 0.5169 | **0.5471** | 0.7463 | 0.78 | 0.7502 | 0.7445 | 0.7438 | 0.7556 | **0.7355** |
| E | E1 | 0.6351 | 0.5965 | 0.6337 | 0.6146 | **0.6824** | 0.626 | 0.6533 | 0.8446 | 0.812 | **0.7746** | 0.8004 | 0.7774 | 0.8089 | 0.8043 |
| | E2 | **0.6477** | 0.6397 | 0.5971 | 0.5563 | 0.5208 | 0.6085 | 0.6301 | 0.6579 | 0.666 | 0.6371 | 0.7305 | 0.7615 | **0.651** | 0.6543 |
| | E3 | **0.9392** | 0.9166 | 0.9152 | 0.9283 | 0.9271 | 0.9188 | 0.9278 | 0.2272 | 0.2303 | 0.2205 | 0.2193 | 0.2273 | **0.1981** | 0.2836 |
| | E4 | 0.3945 | 0.4191 | 0.3901 | 0.453 | 0.3645 | 0.4589 | **0.4596** | 0.768 | 0.6659 | 0.707 | 0.6968 | 0.7457 | 0.6868 | **0.6578** |
| F | F1 | 0.7822 | 0.7746 | 0.792 | 0.7269 | 0.6849 | 0.7832 | **0.7953** | 0.4121 | 0.4363 | 0.4386 | 0.4372 | 0.5242 | 0.4393 | **0.4012** |
| | F2 | 0.9162 | 0.851 | 0.8129 | 0.8765 | **0.9187** | 0.9159 | 0.9089 | **0.1971** | 0.2531 | 0.2546 | 0.2639 | 0.238 | 0.241 | 0.2178 |
| G | G1 | 0.3274 | 0.3509 | 0.3532 | 0.358 | 0.2852 | 0.3841 | **0.3928** | 0.5782 | 0.5803 | 0.5648 | 0.5594 | 0.5492 | 0.5639 | **0.5459** |
| | G2 | 0.4641 | 0.6097 | 0.6056 | 0.6279 | 0.5439 | 0.6357 | **0.647** | 0.3649 | 0.3535 | 0.3287 | 0.352 | 0.3297 | 0.3428 | **0.3152** |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H1 | 0.6457 | 0.6249 | 0.6147 | 0.6444 | 0.5555 | 0.6445 | **0.681** | 0.6728 | 0.6904 | 0.6626 | 0.6747 | 0.7352 | 0.6762 | **0.6517** |
| | H2 | 0.2566 | 0.2844 | 0.3048 | 0.2962 | 0.2641 | 0.3176 | **0.3712** | **0.556** | 0.5797 | 0.5703 | 0.5932 | 0.5563 | 0.5825 | 0.5984 |
| | H3 | 0.4093 | 0.3642 | 0.3488 | 0.3914 | 0.2817 | 0.4156 | **0.4313** | 0.6954 | 0.6838 | 0.6942 | 0.807 | 0.7692 | 0.7516 | **0.6777** |
| | H4 | 0.4503 | 0.3884 | 0.3548 | 0.4547 | 0.4358 | 0.407 | **0.456** | 0.8992 | 0.9338 | 0.8559 | 0.868 | 0.9545 | 0.9159 | **0.8621** |
| I | I1 | 0.3576 | 0.5123 | 0.5346 | 0.5013 | 0.5049 | **0.5669** | 0.529 | 0.6902 | 0.6148 | 0.5029 | 0.5838 | 0.5516 | **0.4851** | 0.5283 |
| | I2 | 0.4701 | 0.4633 | **0.5494** | 0.4859 | 0.1628 | 0.5113 | 0.5301 | 0.1724 | **0.127** | 0.1301 | 0.182 | 0.1726 | 0.1436 | 0.1552 |
| | I3 | 0.3059 | 0.2847 | 0.2682 | 0.2857 | 0.1354 | 0.293 | **0.3122** | 1.2265 | 1.1184 | 1.1464 | 1.1822 | 1.1339 | 1.1697 | **1.1138** |
| | I4 | 0.3123 | 0.4215 | 0.3964 | 0.3914 | 0.3606 | **0.4382** | 0.4273 | 0.7303 | **0.692** | 0.7081 | 0.7706 | 0.7614 | 0.7213 | 0.7641 |
| | I5 | 0.3824 | 0.3691 | 0.3741 | 0.4023 | 0.3544 | 0.4711 | **0.5081** | 0.8708 | 0.8619 | 0.8706 | 0.8607 | 0.7582 | 0.8407 | **0.7815** |
| | I6 | 0.5603 | 0.5311 | 0.5779 | 0.687 | 0.606 | 0.6869 | **0.6969** | 0.5411 | 0.5012 | 0.5134 | 0.4594 | 0.5124 | 0.4674 | **0.4571** |
| | I7 | 0.1323 | 0.2424 | 0.2383 | 0.3001 | 0.2348 | 0.281 | **0.316** | 1.9047 | 1.8909 | 1.9089 | 1.9569 | 1.8907 | 1.9465 | **1.8466** |
| win/tie/loss | | 0/7/24 | 0/5/26 | 0/4/27 | 0/7/24 | 1/4/26 | 2/13/16 | | 2/7/22 | 4/8/19 | 2/11/18 | 1/10/20 | 0/6/25 | 3/11/17 | |

PCC: Pearson correlation coefficient; Lasso: least absolute shrinkage and selection operator; RR: ridge regression; MTLa:multi-task Lasso; cFSGL: convex fused sparse group Lasso; MTR-GL: multi-task regression learning with group Lasso.MTR-ISLR: multi-task regression learning with incoherent sparse and low-rank patterns. ↑ (↓) denotes that larger (smaller) values are better. The results with the greatest performance for each evaluation criterion are emphasized in bold.

**Table S3.** Comparison on top 150 selected features with other feature learning methods

| Group | Dataset | $r^2$ (↑) | | | | | | | RMSE(↓) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PCC | Lasso | RR | MTLa | cFSGL | MTR-GL | MTR-ISLR | PCC | Lasso | RR | MTLa | cFSGL | MTR-GL | MTR-ISLR |
| A | A1 | 0.4249 | 0.3772 | 0.3124 | 0.414 | 0.2631 | 0.3815 | **0.4337** | 0.7058 | 0.7453 | 0.79 | 0.732 | 0.8165 | 0.761 | **0.7017** |
| | A2 | 0.6403 | 0.6321 | 0.6418 | 0.6433 | 0.5795 | 0.6715 | **0.68** | 0.6043 | 0.6284 | 0.5811 | 0.6215 | 0.6529 | 0.5987 | **0.5741** |
| | A3 | 0.4599 | 0.5119 | 0.5274 | 0.5692 | 0.4461 | 0.5869 | **0.6232** | 0.7717 | 0.7299 | 0.722 | 0.735 | 0.7746 | 0.7586 | **0.7195** |
| B | B1 | 0.7195 | 0.7636 | 0.7547 | 0.7667 | 0.7111 | 0.7628 | **0.7914** | 0.6741 | 0.6902 | 0.6803 | 0.7028 | 0.6585 | 0.6644 | **0.6491** |
| | B2 | 0.5788 | 0.6348 | 0.6189 | 0.6418 | 0.6003 | 0.6122 | **0.6372** | 0.5923 | 0.5534 | 0.5591 | 0.558 | 0.5742 | 0.5617 | **0.5457** |
| C | C1 | 0.7231 | 0.7208 | 0.6864 | 0.6829 | 0.7249 | 0.7056 | **0.7284** | **0.8558** | 0.9046 | 0.916 | 0.9509 | 0.8663 | 0.9148 | 1.0663 |
| | C2 | 0.5244 | 0.5686 | 0.5256 | **0.6185** | 0.5965 | 0.5599 | 0.5546 | 0.6393 | 0.6497 | 0.6321 | **0.5805** | 0.5937 | 0.6174 | 0.6759 |
| | C3 | 0.5375 | 0.5386 | 0.5166 | 0.5471 | 0.3778 | 0.5821 | **0.6038** | 0.6404 | 0.6464 | 0.6506 | 0.723 | 0.7395 | 0.6543 | **0.6304** |
| | C4 | 0.4967 | 0.5621 | 0.6002 | 0.5822 | 0.591 | 0.6349 | **0.6509** | 0.6978 | 0.6546 | 0.6762 | 0.6757 | **0.63** | 0.668 | 0.649 |
| D | D1 | 0.7438 | 0.7355 | 0.7519 | 0.8017 | 0.8108 | **0.8257** | 0.7958 | 1.132 | 0.9504 | 0.9679 | 0.9285 | 0.857 | **0.8562** | 0.8668 |
| | D2 | 0.4694 | 0.5369 | 0.5437 | 0.5757 | 0.5442 | 0.5765 | **0.6053** | 0.6558 | 0.5866 | 0.5761 | 0.5742 | 0.5698 | 0.5723 | **0.5674** |
| | D3 | 0.5087 | 0.546 | 0.5366 | 0.5321 | 0.5039 | 0.5492 | **0.5704** | 0.7551 | 0.7527 | 0.7232 | 0.7233 | 0.7474 | 0.7365 | **0.7154** |
| E | E1 | 0.6549 | 0.6288 | 0.6548 | 0.6355 | 0.6636 | 0.6589 | **0.6643** | 0.7984 | 0.8008 | 0.7951 | 0.8186 | **0.7738** | 0.8314 | 0.7891 |
| | E2 | **0.6729** | 0.654 | 0.6528 | 0.5788 | 0.5976 | 0.6144 | 0.6601 | 0.6656 | **0.6579** | 0.6909 | 0.7138 | 0.6906 | 0.6766 | 0.6765 |
| | E3 | **0.9571** | 0.9186 | 0.929 | 0.945 | 0.942 | 0.9515 | 0.9329 | 0.2061 | 0.223 | 0.2222 | 0.2011 | 0.205 | **0.1996** | 0.2551 |
| | E4 | 0.3958 | 0.4498 | 0.4203 | 0.4584 | 0.4012 | 0.4629 | **0.4816** | 0.7278 | 0.662 | 0.717 | 0.6898 | 0.7231 | 0.7075 | **0.6411** |
| F | F1 | 0.8001 | 0.7988 | 0.8169 | 0.7376 | 0.7278 | 0.8093 | **0.8171** | 0.4328 | 0.431 | 0.4386 | 0.448 | 0.4503 | 0.4308 | **0.4297** |
| | F2 | **0.9176** | 0.8525 | 0.8729 | 0.8908 | 0.9088 | 0.9153 | 0.9022 | 0.2534 | 0.2594 | 0.2505 | 0.2318 | **0.2298** | 0.2322 | 0.2363 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| G | G1 | 0.3365 | 0.3517 | 0.3652 | 0.3975 | 0.3053 | 0.4365 | **0.4497** | 0.5694 | 0.582 | 0.5619 | 0.5627 | **0.551** | 0.5676 | 0.5611 |
| | G2 | 0.5829 | 0.6727 | 0.6739 | **0.6862** | 0.6515 | 0.6543 | 0.6734 | 0.3559 | 0.3167 | 0.305 | **0.289** | 0.3299 | 0.2898 | 0.3066 |
| H | H1 | **0.7271** | 0.6962 | 0.7048 | 0.6812 | 0.578 | 0.6745 | 0.7026 | 0.6685 | 0.683 | 0.7061 | **0.6371** | 0.7292 | 0.6499 | 0.6917 |
| | H2 | 0.3612 | 0.3266 | 0.3539 | 0.389 | 0.3243 | 0.3235 | **0.3962** | 0.5414 | 0.5607 | 0.558 | 0.5793 | 0.6529 | 0.5504 | **0.5279** |
| | H3 | 0.4572 | 0.3646 | 0.3559 | 0.4077 | 0.2655 | 0.4217 | **0.4602** | 0.6301 | 0.6436 | 0.6445 | 0.7658 | 0.67 | 0.7681 | **0.6276** |
| | H4 | **0.4837** | 0.4334 | 0.4551 | 0.4609 | 0.4554 | 0.4361 | 0.4721 | 0.8617 | 0.8817 | 0.854 | 0.8682 | 0.9371 | 0.901 | **0.8472** |
| I | I1 | 0.6402 | 0.6766 | 0.6626 | 0.6471 | 0.5986 | 0.674 | **0.6883** | 0.5199 | 0.6714 | 0.5219 | 0.597 | 0.5497 | 0.4755 | **0.4641** |
| | I2 | **0.6139** | 0.5651 | 0.6062 | 0.5272 | 0.1493 | 0.5534 | 0.5428 | **0.1254** | 0.13 | 0.1257 | 0.1423 | 0.1737 | 0.1382 | 0.1515 |
| | I3 | 0.3367 | 0.337 | 0.2903 | **0.354** | 0.2138 | 0.3368 | 0.3515 | 1.2176 | **0.9726** | 1.2132 | 1.2214 | 1.1862 | 1.1258 | 1.0959 |
| | I4 | 0.3531 | 0.4448 | 0.4 | 0.4639 | 0.4713 | 0.4522 | **0.4725** | 0.7031 | **0.672** | 0.7047 | 0.7195 | 0.7143 | 0.7302 | 0.7308 |
| | I5 | 0.4249 | 0.3985 | 0.4459 | 0.4393 | 0.4151 | **0.5485** | 0.5311 | 0.8376 | 0.9068 | 0.7929 | 0.858 | 0.7996 | **0.7456** | 0.7665 |
| | I6 | 0.5659 | 0.6261 | 0.6068 | 0.6961 | 0.5468 | 0.7024 | **0.7056** | 0.551 | 0.4714 | 0.4706 | 0.4502 | 0.5469 | 0.4544 | **0.4405** |
| | I7 | 0.1743 | 0.2741 | 0.3062 | 0.391 | 0.3253 | 0.4031 | **0.4177** | 2.0464 | 1.9536 | 1.8705 | 1.9621 | 2.1205 | 1.9554 | **1.7952** |
| win/tie/loss | | 0/7/24 | 4/8/19 | 0/8/23 | 0/7/24 | 1/10/20 | 0/7/24 | 1/13/17 | | 2/9/20 | 3/9/19 | 0/13/18 | 2/10/19 | 0/8/23 | 2/12/17 |

PCC: Pearson correlation coefficient; Lasso: least absolute shrinkage and selection operator; RR: ridge regression; MTLa:multi-task Lasso; cFSGL: convex fused sparse group Lasso; MTR-GL: multi-task regression learning with group Lasso. MTR-ISLR: multi-task regression learning with incoherent sparse and low-rank patterns. ↑ (↓) denotes that larger (smaller) values are better. The results with the greatest performance for each evaluation criterion are emphasized in bold.

## Supporting Texts

**Code usage of MTR-ISLR.** We designed two programs for demonstration purposes involving different applications in ligand-based virtual screening. All datasets and source codes are freely available for download through our webserver (http://cbi.robotishuman.com/MTR-ISLR/). This provides a general framework for ligand-based virtual screening through multi-task learning with joint feature learning, which allows users to design their own key substructure identification and virtual screening tools on their drug targets of interest. Overall, the pipelines have two major functions:

(1) demo_new: This demonstration program offers a general learning framework for ligand-based virtual screening, and it is formatted in such a way that makes it very easy for users to create their own virtual screening models using our code for their drug targets of interest. Input: Compounds with the format of canonical SMILES and their target-associated bioactivities. Output: Model performance ($r^2$, RMSE). This demo program is implemented as follows: Load compound samples

and their bioactivity values → Encode samples using Pubchem fingerprints → Train multi-task regression learning with incoherent sparse and low-rank patterns (MTR-ISLR) models → Get the model performance.

(2) demo_activity: This demonstration program provides the models for the 31 human GPCRs used in this work. The software was developed to make it easy for users to predict the bioactivities of new compounds acting with these drug targets. Input: Compounds formatted as the canonical SMILES. Output: Bioactivities interacting with the GPCR target of interest. The steps are implemented as follows: Load compounds in the format of canonical SMILES → Produce Pubchem fifingerprints → Get the bioactivity values based on our trained MTR-ISLR models.

## Supporting Data

**Data S1.** Ranking of importance of substructure features from Pubchem fingerprints. (see Data S1.xlsx)

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