A picture containing diagram

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**Supplemental Figure 1**. **Adaptation of PathFX for testing of theoretical methods**. (**A**) To test various theoretical approaches, we adapted PathFX in three ways: first we constructed networks using the optimal distance threshold derived in 2 and then varied the p-value threshold used to select associations discovered by PathFX (left). Next we generated multiple versions of PathFX using a range of distances to explore whether a stringent or relaxed search of the network would correctly associate a drug’s targets to relevant DMEs (middle). Lastly, we used PathFX with the distance and p-value thresholds derived in 2 and then analyzed DME-associated network genes with subsequent multivariate analysis (right). In all cases, PathFX yields an interaction network and a table of ranked phenotype associations. For all diagrams, drugs, network proteins, and phenotypes are represented as triangles, circles, and rounded squares.

A screenshot of a cell phone

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**Supplemental Figure 2**. **Comparison of raw and normalized p-values for true positives and false positives**. (**A**) Distribution of p-values for true and false positive drug associations to DMEs. (**B**) Distribution of normalized p-values for true and false positive drug associations to DMEs. In PathFX, a p-value threshold is derived for each phenotype in the algorithm to prevent study-bias. For instance, the phenotype “cancer” is associated to many network genes and thus a higher level of significance is required to include “cancer” in a drug’s network. This threshold was derived by generating random networks and then measuring the distribution of scores for each phenotype. The normalized p-value represents a network association scaled to the expected p-value discovered from random networks and this process is repeated per phenotype.

**A screenshot of a cell phone

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**Supplemental Figure 3. Performance of three modeling approaches using nested cross validation analysis**. We applied a nested cross validation approach using decision trees (green), random forests (blue), and logistic regression (orange) for 16 DMEs. The remaining 8 DMEs were skipped because they had fewer than 10 positive or 10 negative cases and we considered this to be insufficient data for creating a model. We assessed model performance by F1, ROC, and Accuracy scores. Error bars represent the standard deviation of 500 splits of the data.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **ROC** | **F1** | **Accuracy** |
| dec\_tree | 0.6042 | 0.4639 | 0.6560 |
| rand\_for | 0.5983 | 0.4321 | 0.6487 |
| log\_reg | 0.5954 | 0.4380 | 0.7297 |

**Supplemental Table 1. Average ROC, F1, and Accuracy scores for DMEs used in nested cross-validation**. Scores were averaged across the 16 DME models tested. As described in Supplementary Figure 1, we did not perform model assessment for any cases where we had fewer than 10 positive or fewer than 10 negative cases.

A close up of a map

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**Supplemental Figure 4. ROC curves for all DMEs.** ROC curves are plotted for all 16 DME models.

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**Supplemental Figure 5. Performance values plotted against dataset features per DME.** The average F-score, average precision, average recall, and area under the ROC curve (“ROC value”) are plotted against the total number of true positives (“Total TP”), total number of false positives (“Total FP”), ratio of number of positives to number of false positives (“PosToNegRatio”), fraction of all cases that are true positives (“Fractionpos/total”), total number of genes (“TotalNumGenes’), number of genes appearing in only a single network (“NumSingletonGenes”), and the fraction of genes that are shared between true and false positive drug networks (“FractionSharedGenes”) (**A**). Each dot represents an individual DME and the red line represents a least-squares fit line. The correlation between each variable is provided in (**B**). Darker blue and brighter orange reflect greater negative or positive correlation scores relative to all correlations.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **name** | **Avg FScore** | **Avg Prec** | **Avg Recall** | **ROC value** | **Total FP** | **Total TP** | **Pos To Neg Ratio** | **Fraction pos/total** | **Total Num Genes** | **Num Singleton Genes** | **Fraction Shared Genes** |
| delirium | 0.364 | 0.337 | 0.453 | 0.625 | 55.000 | 17.000 | 0.309 | 0.236 | 15.000 | 0.133 | 0.533 |
| edema | 0.498 | 0.739 | 0.565 | 0.723 | 54.000 | 54.000 | 1.000 | 0.500 | 71.000 | 0.254 | 0.972 |
| gastric\_ulcer | 0.257 | 0.240 | 0.702 | 0.625 | 176.000 | 26.000 | 0.148 | 0.129 | 55.000 | 0.164 | 0.891 |
| hemorrhage | 0.533 | 0.538 | 0.698 | 0.702 | 126.000 | 154.000 | 1.222 | 0.550 | 150.000 | 0.293 | 0.847 |
| hyperlipidemia | 0.221 | 0.173 | 0.580 | 0.652 | 253.000 | 35.000 | 0.138 | 0.122 | 109.000 | 0.248 | 0.706 |
| hypertension | 0.543 | 0.614 | 0.593 | 0.648 | 159.000 | 841.000 | 5.289 | 0.841 | 421.000 | 0.240 | 0.865 |
| myocardial\_infarction | 0.338 | 0.528 | 0.389 | 0.495 | 187.000 | 263.000 | 1.406 | 0.584 | 292.000 | 0.342 | 0.993 |
| myopathy | 0.343 | 0.565 | 0.463 | 0.692 | 152.000 | 36.000 | 0.237 | 0.191 | 223.000 | 0.363 | 0.897 |
| pancreatitis | 0.430 | 0.409 | 0.675 | 0.740 | 197.000 | 128.000 | 0.650 | 0.394 | 172.000 | 0.221 | 0.750 |
| peripheral\_neuropathy | 0.511 | 0.655 | 0.628 | 0.800 | 49.000 | 28.000 | 0.571 | 0.364 | 151.000 | 0.404 | 0.934 |
| pneumonia | 0.517 | 0.643 | 0.609 | 0.778 | 92.000 | 125.000 | 1.359 | 0.576 | 124.000 | 0.234 | 0.960 |
| proteinuria | 0.506 | 0.516 | 0.650 | 0.866 | 68.000 | 27.000 | 0.397 | 0.284 | 66.000 | 0.394 | 0.803 |
| pulmonary\_edema | 0.504 | 0.608 | 0.583 | 0.775 | 50.000 | 18.000 | 0.360 | 0.265 | 36.000 | 0.222 | 0.583 |
| sepsis | 0.336 | 0.273 | 0.638 | 0.702 | 152.000 | 29.000 | 0.191 | 0.160 | 179.000 | 0.285 | 0.855 |
| tardive\_dyskinesia | 0.475 | 0.544 | 0.651 | 0.816 | 175.000 | 35.000 | 0.200 | 0.167 | 43.000 | 0.070 | 0.698 |
| thrombocytopenia | 0.609 | 0.685 | 0.620 | 0.533 | 14.000 | 27.000 | 1.929 | 0.659 | 64.000 | 0.234 | 0.750 |

**Supplemental Table 2. Input data features and performance metrics per DME.**