SUPPLEMENTARY MATERIAL
OWL-NETS: Abstracting Knowledge for Network Inference

Callahan, Baumgartner, Bada, Stefanski, Tripodi, White, and Hunter

1. Acronyms and Definitions

1.1. *Acronyms*

- **AUC:** area under the receiver operating characteristic curve
- **CCDF:** Complementary Cumulative Distribution Function
- **dc:identifier** Dublin Core Element Attributes Identifier
- **IAO:0000219:** Information Artifact Ontology: Denotes relation
- **OBO:** Open Biomedical Ontologies
- **SPARQL:** SPARQL Protocol RDF Query Language
- **OWL:** Web Ontology Language

1.2. *Definitions*

- **Diameter:** shortest distance between the two most distant nodes in the network.
- **Degree Heterogeneity:** is a measure of how much the degree distribution of a network deviates from a "regular network".[1]
- **Disassortativity:** a network is said to have a dissassortative structure if high degree nodes tend to be connected to lower degree nodes.
- **Cliques:** a complete subgraph within a network.
- **Clustering Coefficient:** measure of how much the nodes of a network tend to cluster together.

2. Link Prediction Algorithms

The eight local similarity algorithms, defined consistent with the literature,[2,3] are:

(1) Degree Product: Given two nodes i and j, this measure is calculated as the product of the degree (i.e., the number of connected nodes) of nodes i and j, where k is the node degree:

$$score(i,j) = k_i k_j \tag{1}$$

(2) Common Neighbors: Given two nodes i and j, this measure is calculated as the number of neighbors that are common to both nodes i and j, where $\Gamma(j)$ is the set of nodes connected to node j:

$$score(i,j) = \mid \Gamma(i) \cap \Gamma(j) \mid \tag{2}$$

(3) Jaccard Coefficient:[4] Given two nodes i and j, this measure is calculated as the number of neighbors that are common to both nodes i and j normalized by the number of nodes adjacent to either node i or node j:

$$score(i,j) = \frac{\mid \Gamma(i) \cap \Gamma(j) \mid}{\mid \Gamma(i) \cup \Gamma(j) \mid} \tag{3}$$

(4) Srenson Similarity:[5] Given nodes i and j, this measure is calculated as the number of neighbors that are common to both nodes i and j normalized by the sum of the degrees of node i and node j:

$$score(i, j) = \frac{\mid \Gamma(i) \cap \Gamma(j) \mid}{k_i + k_j} \tag{4}$$

(5) Leicht-Holme-Newman:[6] Given two nodes i and j, this measure is calculated as the number of neighbors that are common to both nodes i and j normalized by the product of the degrees of node i and node j:

$$score(i, j) = \frac{\mid \Gamma(i) \cap \Gamma(j) \mid}{k_i * k_j} \tag{5}$$

(6) Shortest Paths: Given two nodes i and j, this measure is calculated as the reciprocal of the length of the shortest path from node i to node $j(\sigma(i, j))$:

$$score(i, j) = \frac{1}{\sigma(i, j)} \tag{6}$$

A score of zero is given for all node pairs not connected by a path.

(7) Resource Allocation:[7] Given two nodes i and j, this measure is calculated as the sum of the reciprocal of the degrees of nodes adjacent to both nodes i and j:

$$score(i, j) = \sum_{z \in \Gamma(i) \cap \Gamma(j)} \frac{1}{k_z} \tag{7}$$

(8) Adamic-Advar:[8] Given two nodes i and j, this measure is calculated as the sum of the reciprocal of the log of the degrees of the nodes adjacent to both nodes i and j:

$$score(i, j) = \sum_{z \in \Gamma(i) \cap \Gamma(j)} \frac{1}{\log(k_z)} \tag{8}$$

The two global similarity algorithms, defined consistent with the literature,[9] are:

(1) Katz:[10] Given an unweighted adjacency matrix A, $A_{i,j}$ is one if there is a link between nodes i and j and zero if there is not. Each element of A_{ij}, A^k has value equal to the number of walks with length k between nodes i and j:

$$score(i, j) = \sum_{k=1}^{\infty} \beta^k A_{ij}^k \tag{9}$$

where β, must be lower than the largest eigenvector of matrix A, that is used to give shorter paths more weight. Consistent with the literature,[11] a value of $\beta = 0.001$ was used.

(2) Rooted PageRank: A random walker starts from node i and randomly moves to a neighbor of node i. The walker then has a probability of $1 - \alpha$ for teleporting back to node i. Consistent with the literature,[11] a value of $\alpha = 0.15$ was used.

Table S1. Descriptive Characteristics by Network Representation

Property	OWL	OWL-NETS	p-value
Nodes	1578.400 (155.850)	247.950 (22.741)	< 0.0001
Edges	4110.930 (445.103)	1130.100 (153.514)	< 0.0001
Average Degree	5.204 (0.091)	9.083 (0.473)	< 0.0001
Density	0.003 (0.000)	0.037 (0.002)	0.002
Diameter	10.000 (0.000)	5.880 (0.325)	< 0.0001
Clustering Coefficient	0.067 (0.005)	0.338 (0.013)	0.013
Degree Assortativity	-0.223 (0.001)	-0.122 (0.019)	0.019
Degree Heterogeneity	13.684 (1.542)	2.354 (0.185)	< 0.0001
Number of Shortest Paths	5694.170 (1054.645)	683.680 (116.755)	< 0.0001
Average Shortest Path Length	3.760 (0.039)	2.934 (0.048)	< 0.0001
Number of Cliques	3532.050 (376.901)	703.110 (95.554)	< 0.0001

Table S2. Descriptive Characteristics by Network Representation and Query

Property	Q2:OWL	Q2:OWL-NETS	Q3:OWL	Q3:OWL-NETS
Nodes	840	59	22,679	1783
Edges	1426	59	33,848	3940
Average Degree	3.419	2.000	2.980	4.420
Density	0.0040	0.0344	0.0001	0.0020
Diameter	13	4	9	18[a]
Degree Assortativity	-0.193	-0.630	-0.124	-0.308
Degree Heterogeneity	8.789	4.533	558.463	6.673
Number of Shortest Paths	2,683	202	91,483	8,986[a]
Average Shortest Path Length	4.06	3.19	4.13	6.54[a]

*Query (Q). All descriptives were run on the undirected versions of the networks.

[a]Query 3:OWL-NETS statistics were derived on the largest connected component.

Table S3. Query 2 Link Prediction Run-Time

Algorithm	OWL	OWL-NETS
Degree Product	00:00:07	00:37:42
Shortest Path	00:00:10	01:49:08
Common Neighbors	00:00:07	00:31:47
Jaccard Coefficient	00:00:07	00:32:04
Sorenson Similarity	00:00:07	00:32:09
Leicht-Holme-Newman	00:00:07	00:32:09
Adamic Advar	00:00:08	00:32:51
Resource Allocation	00:00:07	00:32:36
Katz	00:00:30	08:12:51
Rooted Page Rank	00:01:00	12:16:21

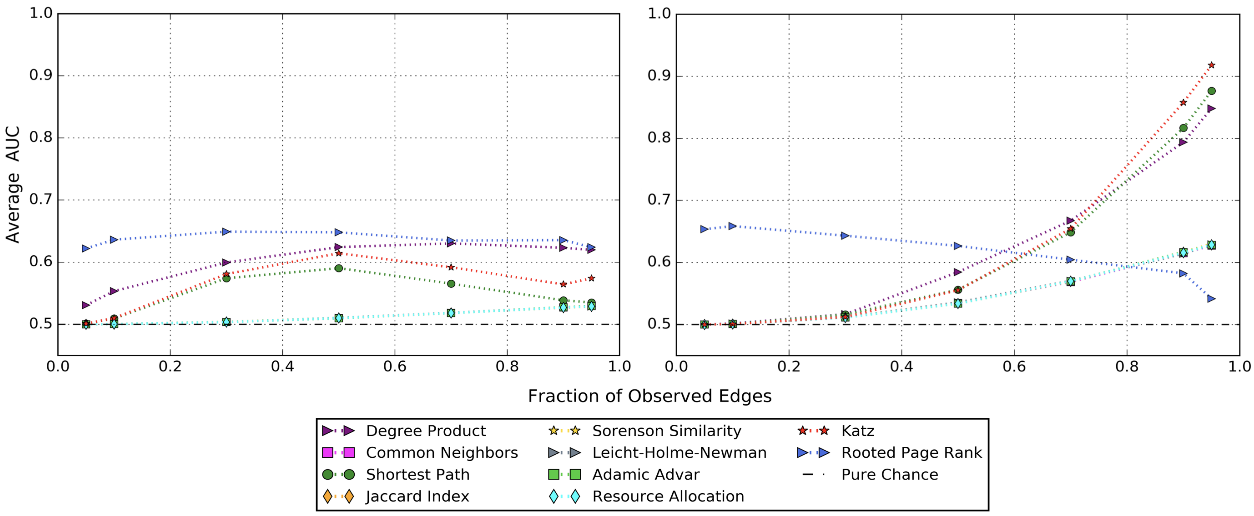

Fig. S1. Comparison of Link Prediction Methods by Network. (left) The original OWL representation network and (right) the OWL-NETS abstraction networks created from Query 2 (Table1).

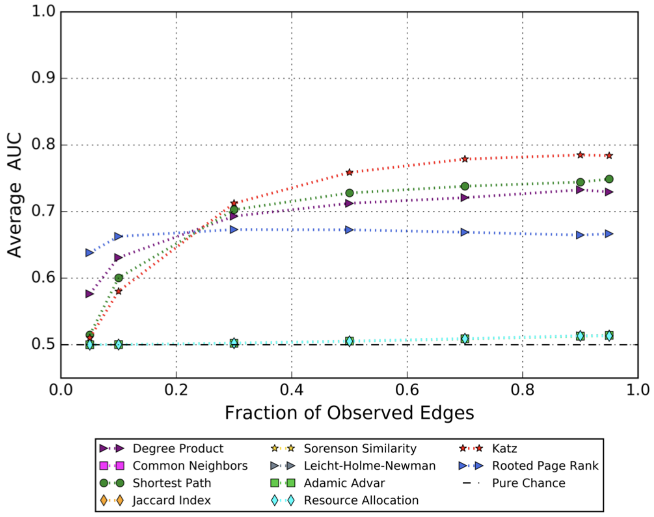

Fig. S2. Link Prediction Methods. The OWL-NETS abstraction networks created from Query 3 (Table1).

Table S4. Top Scoring Edges from the Query 3 OWL-NETS Abstraction Networks (n=6 edges)

Node 1	Node 2	Description
AG-1067[a]	MMP2[b]	AGI-1067 is derived from probucol, which has been shown to decrease MMP-2 expression and activity in Apolipoprotein E-deficient mice.[12]
DB03683[a]	APAF1[b]	DB03683a targets MMP9 through an unknown mechanism. Downregulation of MMP9 induces APAF1 expression.[13]
celiprolol[a]	CYCS[b]	Celiprolol is an investigational drug used to treat hypertension. Cytochrome c has been shown to mediate hypertension in rats and in humans.[14,15]
1454838[c]	TF[b]	TF binds to and transports iron. Iron is required for the proliferation of multiple myeloma cells. CD147 (1454838) is overexpressed in multiple myeloma cells and is positively correlated with cell proliferation.[16,17]
DB04513[a]	RAF1[b]	DB04513 targets Calmodulin 1, which can regulate the threshold for activation of the Ras/Raf/MEK/ERK signaling pathway.[18]
CXCL12[b]	DB07691[a]	DB07691 is an n-phenylbenzamide, which can inhibit the Mitochondrial Permeability Transition Pore whose continual opening is associated with mitochondrial dysfunction. CXCL12 regulates mitochondria association around the MTOC (microtubule organizing center).[19,20]

[a]DrugBank entity (DrugBank ID used for experimental compounds); [b]Uniprot entity (gene symbol shown); [c]Reactome entity (database identifier).

References

1. E. Estrada (ed.), *The structure of complex networks: theory and applications* (Oxford University Press, 2012).
2. A. Clauset, C. Moore and M. E. J. Newman, *Nature* **453**, 98 (2008).
3. S. Soundarajan and J. Hopcroft, Using community information to improve the precision of link prediction methods, in *Proceedings of the 21st International Conference on World Wide Web, ACM*, 2012.
4. P. Jaccard, *Bull Soc Vaudoise Sci Nat* **37**, 547 (1901).
5. J. A. Hanley and B. J. McNeil, *Biol Skr* **5**, 1 (1948).
6. E. A. Leicht, P. Holme and M. E. Newman, *Physical Review E* **73**, p. 026120 (2006).
7. T. Zhou, L. Lu and Y.-C. Zhang, *Eur Phys J B* **71**, 623 (2009).
8. L. A. Adamic and E. Adar, *Soc Networks* **25**, 211 (2003).
9. R. Guns, *J Data Inform Sci* **1**, 59 (2016).
10. L. Katz, *Psychometrika* **18**, 39 (1953).
11. D. Liben-Nowell and J. Kleinberg, *J. Am. Soc. Inf. Sci.* **58**, 1019 (2007).
12. B. J. Wu, N. D. Girolamo, K. Beck, C. G. Hanratty, K. Choy, J. Y. Hou, M. R. Ward and R. Stocker, *J Pharmacol Exp Ther* **321**, 477 (2007).
13. C. S. Gondi, N. Kandhukuri, D. H. Dinh, W. C. Olivero, M. Gujrati and J. S. Rao, *Int J Oncol* **33**, 783 (2008).
14. C. P. Venditti, M. C. Harris, D. Huff, I. Peterside, D. Munson, H. S. Weber, J. Rome, E. M. Kaye, S. Shanske and S. Sacconi, *J Inherit Metab Dis* **27**, 735 (2004).
15. W.-Z. Ying and P. W. Sanders, *Kidney Int* **59**, 662 (2001).
16. B. K. Arendt, D. K. Walters, X. Wu, R. C. Tschumper, P. M. Huddleston, K. J. Henderson, A. Dispenzieri and D. F. Jelinek, *Leukemia* **26**, 2286 (2012).
17. K. VanderWall, T. R. Daniels-Wells, M. Penichet and A. Lichtenstein, *J Inherit Metab Dis* **18**, 449 (2013).
18. N. Agell, O. Bachs, N. Rocamora and P. Villalonga, *Cell Signal* **14**, 649 (2002).
19. G. Morlino, O. Barreiro, F. Baixauli, J. Robles-Valero, J. Gonzalez-Granado, R. Villa-Bellosta, J. Cuenca, C. O. Sanchez-Sorzano, E. Veiga, N. B. Martn-Cfreces and F. Snchez-Madrid, *Mol Cell Biol* **34**, 1412 (2014).
20. S. Roy, J. ileikyt, B. Neuenswander, M. P. Hedrick, T. D. Chung, J. Aub, F. J. Schoenen, M. A. Forte and P. Bernardi, *ChemMedChem* **11**, 283 (2016).