

# Hetnet connectivity search provides rapid insights into how two biomedical entities are related

This manuscript ([permalink](#)) was automatically generated from [greenelab/connectivity-search-manuscript@37f8433](#) on June 23, 2020.

## Authors

---

### Manuscript in preparation

The authorship information below is incomplete and preliminary. This notice will be updated once all contributors meeting [authorship criteria](#) have added themselves to [metadata.yaml](#).

- **Daniel S. Himmelstein**

 [0000-0002-3012-7446](#) ·  [dhimmel](#) ·  [dhimmel](#)

Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America · Funded by GBMF4552

## Abstract

---

Hetnets, short for “heterogeneous networks”, contain multiple node and relationship types and offer a way to encode biomedical knowledge. For example, Hetionet connects 11 types of nodes — including genes, diseases, drugs, pathways, and anatomical structures — with over 2 million edges of 24 types. Previously, we trained a classifier to repurpose drugs using features extracted from Hetionet. The model identified types of paths between a drug and disease that occurred more frequently between known treatments.

For many applications however, a training set of known relationships does not exist; Yet researchers would still like to know how two nodes are meaningfully connected. For example, users may want to know not only how metformin is related to breast cancer, but also how the GJA1 gene might be involved in insomnia. Therefore, we developed hetnet connectivity search to propose the most important paths between any two nodes.

The algorithm behind connectivity search identifies types of paths that occur more frequently than would be expected by chance (based on node degree alone). We implemented the method on Hetionet and provide an online interface at <https://het.io/search>. Several optimizations were required to precompute significant instances of node connectivity at scale. We provide an open source implementation of these methods in our new Python package named [hetmatpy](#).

To validate the method, we show that it identifies much of the same evidence for specific instances of drug repurposing as the previous supervised approach, but without requiring a training set.

# Introduction

A *network* (also known as a [graph](#)) is a conceptual representation of a group of entities — called *nodes* — and the relationships between them — called *edges*. Typically, a network has only one type of node and one type of edge. But in many cases, it is necessary to be able to distinguish between different types of entities and relationships.

## Hetnets

A *hetnet* (short for **heterogeneous information network** [[1](#)]) is a network where nodes and edges have type. The ability to differentiate between different types of entities and relationships allows a hetnet to accurately describe more complex data. Hetnets are particularly useful in biomedicine, where it is important to capture the conceptual distinctions between various concepts, such as genes and diseases, or upregulation and binding.

The types of nodes and edges in a hetnet are defined by a schema, referred to as a metagraph. The metagraph consists of metanodes (types of nodes) and metaedges (types of edges). Note that the prefix *meta* is used to refer to type (e.g. compound), as opposed to a specific node/edge/path itself (e.g. acetaminophen).

## Hetionet

[Hetionet](#) is a knowledge graph of human biology, disease, and medicine, integrating information from millions of studies and decades of research. Hetionet v1.0 combines information from [29 public databases](#). The network contains 47,031 nodes of [11 types](#) (Table [1](#)) and 2,250,197 edges of [24 types](#).

**Table 1: Node types in Hetionet** The abbreviation, number of nodes, and description for each of the 11 metanodes in Hetionet v1.0.

Metanode	Abbr	Nodes	Description
Anatomy	A	402	Anatomical structures, excluding structures that are known not to be found in humans. From <a href="#">Uberon</a> .
Biological Process	BP	11381	Larger processes or biological programs accomplished by multiple molecular activities. From <a href="#">Gene Ontology</a> .
Cellular Component	CC	1391	The locations relative to cellular structures in which a gene product performs a function. From <a href="#">Gene Ontology</a> .
Compound	C	1552	Approved small molecule compounds with documented chemical structures. From <a href="#">DrugBank</a> .
Disease	D	137	Complex diseases, selected to be distinct and specific enough to be clinically relevant yet general enough to be well annotated. From <a href="#">Disease Ontology</a> .

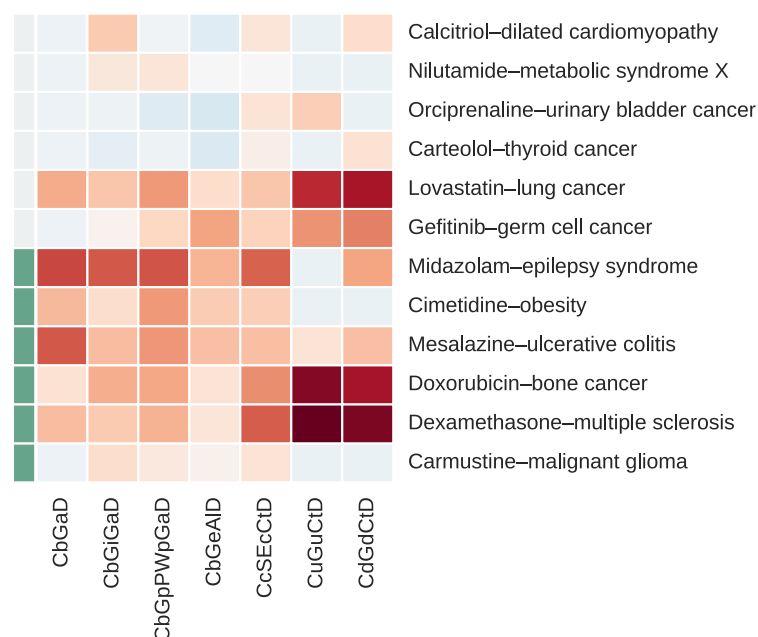
Metanode	Abbr	Nodes	Description
Gene	G	20945	Protein-coding human genes. From <a href="#">Entrez Gene</a> .
Molecular Function	MF	2884	Activities that occur at the molecular level, such as “catalysis” or “transport”. From <a href="#">Gene Ontology</a> .
Pathway	PW	1822	A series of actions among molecules in a cell that leads to a certain product or change in the cell. From <a href="#">WikiPathways</a> , <a href="#">Reactome</a> , and Pathway Interaction Database.
Pharmacologic Class	PC	345	“Chemical/Ingredient”, “Mechanism of Action”, and “Physiologic Effect” FDA class types. From <a href="#">DrugCentral</a> .
Side Effect	SE	5734	Adverse drug reactions. From <a href="#">SIDER</a> / <a href="#">UMLS</a> .
Symptom	S	438	Signs and Symptoms (i.e. clinical abnormalities that can indicate a medical condition). From the <a href="#">MeSH ontology</a> .

Hetionet provides a foundation for building hetnet applications. It unifies data from several different, disparate sources into a single, comprehensive, accessible, common-format network. The database is publicly accessible without login at <https://neo4j.het.io>. The Neo4j graph database enables querying Hetionet using the Cypher language, which was designed to interact with networks where nodes and edges have both types and properties.

One limitation that restricts the applicability of Hetionet is incompleteness. In many cases, Hetionet v1.0 includes only a subset of the nodes from a given resource. For example, the Disease Ontology contains over 9,000 diseases [2], while Hetionet includes only 137 diseases [3]. Nodes were excluded to avoid redundant or overly specific nodes, while ensuring a minimum level of connectivity for compounds and diseases. See the [Project Rephetio methods](#) for more details [4]. Nonetheless, Hetionet v1.0 remains one of the most comprehensive and integrative networks that consolidates biomedical knowledge into a manageable number of node and edge types. Other integrative resources, some still under development, include [Wikidata](#) [5], [SemMedDB](#) [6,7,8], [SPOKE](#), and [DRKG](#).

## Rephetio

Project Rephetio is the name of the [study](#) that created Hetionet and applied it repurpose drugs [4]. This project [predicted](#) the probability of drug efficacy for 209,168 compound–disease pairs. The approach learned which types of paths occur more or less frequently between known treatments than non-treatments (Figure 1). To train the model, Rephetio created [PharmacotherapyDB](#), a physician-curated catalog of 755 disease-modifying treatments [9].



**Figure 1: Supervised machine learning approach from Project Rephetio.** This figure visualizes the feature matrix used by Project Rephetio to make supervised predictions. Each row represents a compound–disease pair. The top half of rows correspond to known treatments (i.e. positives), while the bottom half correspond to non-treatments (i.e. negatives, not known to be treatments in PharmacotherapyDB). Here, an equal number of treatments and non-treatments are shown, but in reality the problem is heavily imbalanced. Project Rephetio scaled models to assume a positive prevalence of 0.36% [4,10]. Each column represents a metapath, labeled with its abbreviation.

Feature values are DWPCs (transformed and standardized), which assess the connectivity along the specified metapath between the specific compound and disease. Maroon colored values indicate above-average connectivity, whereas blue values indicate below average connectivity. In general, positives have greater connectivity for the selected metapaths than negatives. Rephetio used a logistic regression model to learn the effect of each type of connectivity (feature) on the likelihood that a compound treats a disease. The model predicts whether a compound–disease pair is a treatment based on its features, but requires supervision in the form of known treatments.

## TODO: Other works

<https://github.com/greenelab/hetmech/issues/56>

Network embeddings edge2vec [11], metapath2vec [12], HINE [13].

[14] training node pairs to important metapaths (Forward Stagewise Path Generation). MetaExp [15] user selects two sets of nodes. MetaExp detects metapaths and interacts with the user to progressively refine metapaths.

## Unsupervised connectivity search

## Results

---

### Connectivity Search Webapp

We created the connectivity search webapp available at <https://het.io/search/>. The tool is free to use, without any login or authentication. The purpose is let users quickly explore how any two nodes in Hetionet v1.0 might be related. The workflow is based around showing the user the most important metapaths and paths for a pair of query nodes.

The design guides the user through selecting a source and target node (Figure 2A). The webapp returns metapaths, scored by whether they occurred more than expected based on network degree (Figure 2B). Users can proceed by requesting the specific paths for each metapath, which are placed in a unified table sorted according to their path score (Figure 2C). Finally, the webapp produces publication-ready visualizations containing user-selected paths (Figure 2D).

Filters

select all deselect all

Gene Compound Anatomy Disease Symptom  
 Side Effect Biological Process Cellular Component  
 Molecular Function Pathway Pharmacologic Class

Source Node

Alzheimer's disease

Target Node

name or identifier

- transcription factor complex 8
- DNA-templated transcription, initiation 7
- mRNA Processing 7
- transcription initiation from RNA polymerase II promoter 7
- Circadian rhythm related genes 7
- protein serine/threonine kinase activity 7

A. Node Search

27 results, 7 selected precomputed only expand

metapath	path count	adjusted p-value
	343	$4.8 \times 10^{-5}$
	479	$1.2 \times 10^{-3}$
	360	$2.3 \times 10^{-3}$
	997	$2.9 \times 10^{-2}$
	191	$5.9 \times 10^{-2}$
	195	$6.6 \times 10^{-2}$
	7	$8.5 \times 10^{-2}$
	5	$1.8 \times 10^{-1}$
	13	$2.1 \times 10^{-1}$
	181	$2.5 \times 10^{-1}$

10 << < 1 of 3 > >>

B. Metapaths

425 results, 7 selected, 1 highlighted expand

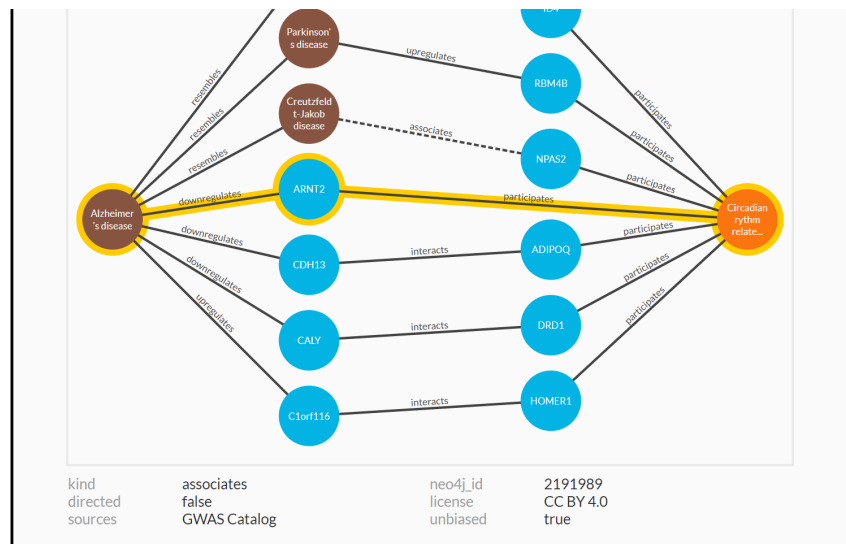
metapath	path	path score	% of DWPC
DuGiGpPW	35.2	13.3	
DrDaGpPW	29.3	42.7	
DdGiGpPW	28.3	6.6	
DrDuGpPW	28.1	26.3	
DdGiGpPW	27.9	6.5	
DdGpPW	27.3	36.4	
DrDuGpPW	24.5	22.9	
DdGiGpPW	21.6	5.0	
DaGiGpPW	19.0	6.5	
DdGiGpPW	18.5	4.3	

10 << < 1 of 43 > >>

C. Paths

reset unpin pin fit grid .svg

15 nodes, 20 edges 640 x 480



D. Graph

**Figure 2: Using the connectivity search webapp to explore the pathophysiology of Alzheimer's disease.** This figure shows an example user workflow for <https://het.io/search/>.

**A.** The user selects two nodes. Here, the user is interested in Alzheimer's disease, so [selects this](#) as the source node. The user limits the target node search to metanodes relating to gene function. The target node search box suggests nodes, sorted by the number of significant metapaths. When the user types in the target node box, the matches reorder based on search word similarity. Here, the user becomes interested in how the circadian rhythm might relate to Alzheimer's disease.

**B.** The webapp returns metapaths between Alzheimer's disease and the circadian rhythm pathway. The user unchecks "precomputed only" to compute results for all metapaths with length  $\leq 3$ , not just those that surpass the database inclusion threshold. The user sorts by adjusted  $p$ -value and [selects](#) 7 of the top 10 metapaths.

**C.** Paths for the selected metapaths are ordered by their path score. The user selects 7 paths to show in the graph visualization and highlights a single path involving *ARNT2* for emphasis.

**D.** A subgraph displays the previously selected paths. The user improves on the automated layout by repositioning nodes. Clicking an edge displays its properties, informing the user that association between Creutzfeldt-Jakob disease and *NPAS2* was detected by GWAS.

## Hetmatpy Package

We created the hetmatpy Python package, available on [GitHub](#) and [PyPI](#) under the permissive BSD-2-Clause Plus Patent License. This package provides a matrix-based utilities for hetnets.

## DWPC null distribution

To assess connectivity between a source and target node, we use the DWPC (degree-weighted path count) metric. The DWPC is similar to path count (number of paths between the source and target node along a given metapath), except that it downweights paths through high degree nodes. Rather than using the raw DWPC for a source-metapath-target combination, we transform the DWPC across all source-target node pairs for a metapath to yield a distribution that is more compact and amenable to modeling [16].

Previously, we had no technique for detecting whether a DWPC value was exceptional. One possibility is to evaluate the DWPCs for all pairs of nodes and select the top scores (e.g. the top 5% of DWPCs). Another possibility is to pick a transformed DWPC score as a cutoff. The shortcomings of these methods are twofold. First, neither the percentile nor absolute value of a DWPC has inherent meaning. To select transformed DWPCs greater than 6, or alternatively the top 1% of DWPCs, is arbitrary. Second, comparing DWPCs between node pairs fails to account for the situation where high-degree node pairs are likely to score higher, solely on account of their degree (TODO: figure).



To address these shortcomings, we developed a method to compute the right-tail  $p$ -value of a DWPC.  $p$ -values have a broadly understood interpretation — in our case, the probability that a DWPC equal to or greater than the observed DWPC could occur under a null model. By tailoring the null distribution for a DWPC to the degree of its source and target node, we account for degree effects when determining the significance of a DWPC.

## Enriched metapaths

27 results, 7 selected

.csv precomputed only collapse

Null DWPC distribution information

metapath	path count	adjusted $p$ -value	$p$ -value	DWPC	source degree	target degree	# DWPC's	# non-0 DWPC's	non-0 mean	non-0 $\sigma$	Neo4j Actions
	343	$4.8 \times 10^{-5}$	$2.0 \times 10^{-6}$	3.8	250	201	5,200	5,200	3.0	0.2	<a href="#">browser</a>
	479	$1.2 \times 10^{-3}$	$5.1 \times 10^{-5}$	2.8	196	201	200	200	2.0	0.2	<a href="#">browser</a>
	360	$2.3 \times 10^{-3}$	$9.5 \times 10^{-5}$	3.6	250	201	5,400	5,400	2.9	0.2	<a href="#">browser</a>
	997	$2.9 \times 10^{-2}$	$1.2 \times 10^{-3}$	2.6	20	201	800	800	1.4	0.3	<a href="#">browser</a>
	191	$5.9 \times 10^{-2}$	$2.5 \times 10^{-3}$	3.6	250	201	5,400	5,400	3.0	0.2	<a href="#">browser</a>
	195	$6.6 \times 10^{-2}$	$2.8 \times 10^{-3}$	3.6	250	201	5,200	5,200	3.0	0.2	<a href="#">browser</a>
	7	$8.5 \times 10^{-2}$	$3.5 \times 10^{-3}$	3.6	3	201	2,800	1,428	1.5	0.7	<a href="#">browser</a>
	5	$1.8 \times 10^{-1}$	$5.9 \times 10^{-2}$	4.0	250	201	5,200	5,021	2.8	0.7	<a href="#">browser</a>
	13	$2.1 \times 10^{-1}$	$8.6 \times 10^{-3}$	2.8	3	201	2,800	2,718	1.1	0.5	<a href="#">browser</a>
	181	$2.5 \times 10^{-1}$	$1.0 \times 10^{-2}$	3.6	250	201	5,400	5,400	3.0	0.2	<a href="#">browser</a>

10

<< < 1 of 3 > >>

**Figure 3: Expanded metapath details from the connectivity search webapp.** This is the expanded view of the [metapath table](#) in [2B](#).

Figure [3](#) shows the information used to compute  $p$ -value for enriched metapaths. The table includes the following columns:

- **path count:** The number of paths between the source and target node of the specified metapath
- **adjusted  $p$ -value:** A measure of the significance of the DWPC that indicates whether more paths were observed than expected due to random chance. Compares the DWPC to a null distribution of DWPCs generated from degree-preserving permuted networks. Bonferroni-adjusted for the number of metapaths with the same source metanode, target metanode, and length.
- **$p$ -value:** A measure of the significance of the DWPC that indicates whether more paths were observed than expected due to random chance. Compares the DWPC to a null distribution of DWPCs generated from degree-preserving permuted networks. Not adjusted for multiple comparisons (i.e. when multiple metapaths are assessed for significant connectivity between the source and target node).
- **DWPC:** Degree-Weighted Path Count — Measures the extent of connectivity between the source and target node for the given metapath. Like the path count, but with less weight given to paths along high-degree nodes.
- **source degree:** The number of edges from the source node that are of the same type as the initial metaedge of the metapath.
- **target degree:** The number of edges from the target node that are of the same type as the final metaedge of the metapath.
- **# DWPCs:** The number of DWPCs calculated on permuted networks used to generate a null distribution for the DWPC from the real network. Permuted DWPCs are aggregated for all permuted node pairs with the same degrees as the source and target node.
- **# non-0 DWPCs:** The number of permuted DWPCs from '# of DWPCs' column that were nonzero. Nonzero DWPCs indicate at least one path between the source and target node existed in the permuted network.
- **non-0 mean:** The mean of nonzero permuted DWPCs. Used to generate the gamma-hurdle model of the null DWPC distribution.

- **non-0  $\sigma$** : The standard deviation of nonzero permuted DWPCs. Used to generate the gamma-hurdle model of the null DWPC distribution.
- **Neo4j Actions**: A Cypher query that users can run in the [Neo4j browser](#) to show paths with the largest DWPCs for the metapath.

## Enriched paths

## Comparison to Rephetio

## Detecting Mechanisms of Action for Indications

Assess ability to predict paths in <https://github.com/SuLab/DrugMechDB>

## Use cases

## Discussion

---

STUB: Contributions of this work:

- search engine for hetnet connectivity between two nodes, realtime results
- interactive webapp and user interface for displaying metapaths, paths, and subgraphs.
- optimized methods for computing DWPCs using matrix multiplication
- method for estimating  $p$ -values for a DWPC, based on null DWPCs computed from permuted hetnets.
- the hetmatpy Python package and HetMat data structure that provide a highly-optimized computational infrastructure to make this possible.

STUB: Future work:

- node set transformations
- [improved DWPC scaling](#)
- longer metapaths
- auto-detection of informative metapaths

## Methods

---

### The HetMat awakens

At the core of the hetmatpy package is the HetMat data structure for storing and accessing the network. HetMats are stored on disk as a directory, which by convention uses a `.hetmat` extension. A HetMat directory stores a single heterogeneous network, whose data resides in the following files.

1. A `metagraph.json` file stores the schema, defining which types of nodes and edges comprise the hetnet. This format is defined by the [hetnetpy](#) Python package. Hetnetpy was originally developed with the name `hetio` during prior studies [4,17], but we [renamed](#) it to `hetnetpy` for better disambiguation from `hetmatpy`.
2. A `nodes` directory containing one file per node type (metanode) that defines each node. Currently, `.tsv` files where each row represents a node are supported.
3. An `edges` directory containing one file per edge type (metadata) that encodes the adjacency matrix. The matrix can be serialized using either the Numpy dense format (`.npy`) or SciPy sparse format (`.sparse.npz`).

For node and edge files, compression is supported as detected from `.gz`, `.bz2`, `.zip`, and `.xz` extensions. This structure of storing a hetnet supports selectively reading nodes and edges into memory. For example, a certain computation may only require access to a subset of the node and edge types. By only loading the required node and edge types, we reduce memory usage and read times.

Additional subdirectories, such as `path-counts` and `permutations`, store data generated from the HetMat. By using consistent paths for generated data, we avoid recomputing data that already exists on disk. A HetMat directory can be zipped for archiving and transfer. Users can selectively include generated data in archives. Since the primary application of HetMats is to generate computationally demanding measurements on hetnets, the ability to share HetMats with precomputed data is paramount.

The `HetMat` class implements the above logic. A `hetmat_from_graph` function creates a HetMat object and directory on disk from the pre-existing `hetnetpy.hetnet.Graph` format.

We converted Hetionet v1.0 to HetMat format and uploaded the `hetionet-v1.0.hetmat.zip` archive to the [Hetionet data repository](#).

### Computing DWPCs with matrix multiplication

Prior to this study, we used two implementations for computing DWPCs. The first is a pure Python implementation available in the `hetnetpy.pathtools.DWPC` function [17]. The second uses a Cypher query, prepared by `hetnetpy.neo4j.construct_dwpc_query`, that is executed by the Neo4j database [4,18]. Both of these implementations require traversing all paths between the source and target node. Hence, they are computationally cumbersome despite optimizations [19].

An alternative approach counts paths by multiplying adjacency matrixes. However, this approach actually counts walks, since it includes sequences of edges that traverse a single node (i.e. trail) or edge (i.e. walk) multiple times. When computing network-based features to quantify the relationship between a source and target node, we would like to exclude traversing duplicate nodes (i.e. paths, not trails nor walks) [20]. Therefore, we invented a suite of algorithms to compute true path counts and DWPCs using matrix multiplication.

TODO: Describe the suite of DWPC algorithms. From the categorize function, there are:

- no\_repeats
- disjoint
- short\_repeat
- long\_repeat
- BAAB
- BABA
- repeat\_around
- interior\_complete\_group
- disjoint\_groups
- other

Include information on what lengths of metapath we have completely solved this for. Mention testing against existing methods.

Mention approximations. Also note independent approximation work at [https://github.com/mmayers12/hetnet\\_ml](https://github.com/mmayers12/hetnet_ml)

Discuss caching strategies, sequential versus recursive

Runtime comparison to show the speedup. Rephetio computed a portion of in XX time

From [21]:

We reduced the time to compute DWPC over nearly 1200 metapaths from roughly four-and-a-half days to roughly one hour and thirty-seven minutes

175-fold, which underestimates since Rephetio did not compute the full DWPC matrix and benefited from concurrency.

## Permuted hetnets

In order to generate a null distribution for a DWPC, we rely on DWPCs computed from permuted hetnets. We derive permuted hetnets from the unpermuted network using the XSwap algorithm [22]. XSwap randomizes edges while preserving node degree. Therefore, it's ideal for generating null distributions that retain general degree effects, but destroy the actual meaning of edges. We adapt XSwap to hetnets by applying it separately to each metaedge [???,4,23].

Project Rephetio created 5 permuted hetnets [4,23], which were used to generate a null distribution of classifier performance for each metapath-based feature. Here, we aim to create a null distribution for individual DWPCs, which requires vastly more permuted values to estimate with accuracy. Therefore, we generated 200 permuted hetnets (archive). More recently, we also developed the xswap Python package, whose optimized C/C++ implementation will enable future research to generate even larger sets of permuted networks [???].

## Degree-grouping of node pairs

For each of the 200 permuted networks and each of the 2,205 metapaths, we computed the entire DWPC matrix (i.e. all source nodes  $\times$  target nodes). Therefore, for each actual DWPC value, we computed 200 permuted DWPC values. Because permutation preserves only node degree, DWPC values among nodes with the same source and target degrees are equivalent to additional

permutations. We greatly increased the effective number of permutations by grouping DWPC values according to node degree, affording us a superior estimation of the DWPC null distribution.

We have applied this *degree-grouping* approach previously when calculating the prior probability of edge existence based on the source and target node degrees [???,24]. But here, we apply *degree-grouping* to null DWPCs. The result is that the null distribution for a DWPC is based not only on permuted DWPCs for the corresponding source–metapath–target combination, but instead on all permuted DWPCs for the source-degree–metapath–target-degree combination.

The “# DWPCs” column in Figure 3 illustrates how degree-grouping inflates the sample size of null DWPCs. The  $p$ -value for the *DaGiGpPW* metapath relies on the minimum number of null DWPCs (200), since no other disease besides Alzheimer’s had 196 *associates* edges (source degree) and no other pathway besides circadian rhythm had 201 *participates* edges (target degree). However, for other metapaths with over 5,000 null DWPCs, degree-grouping increased the size of the null distribution by a factor of 25. In general, source–target node pairs with lower degrees receive the largest sample size multiplier from degree-grouping. This is convenient since low degree nodes also tend to produce the highest proportion of zero DWPCs, by virtue of low connectivity. Consequently, degree-grouping excels where it is needed most.

One final benefit of degree-grouping is that reduces the disk space required to store null DWPC summary statistics. For example, with 20,945 genes in Hetionet v1.0, there exists 438,693,025 gene pairs. Gene nodes have 302 distinct degrees for *interacts* edges, resulting in 91,204 degree pairs. This equates to an 4,810-fold reduction in the number of summary statistics that need to be stored to represent the null DWPC distribution for a metapath starting and ending with a *Gene–interacts–Gene* metaedge.

We store the following null DWPC summary statistics for each metapath–source-degree–target-degree combination: total number of null DWPCs, total number of nonzero null DWPCs, sum of null DWPCs, sum of squared null DWPCs, and number of permuted hetnets. These values are sufficient to estimate the  $p$ -value for a DWPC, by either fitting a gamma-hurdle null distribution or generating an empiric  $p$ -value. Furthermore, these statistics are additive across permuted hetnets. Their values are always a running total and can be updated incrementally as statistics from each additional permuted hetnet become available.

We generated null DWPC summary statistics for all Hetionet metapaths with length  $\leq 3$ , and bundled them into HetMat archives by metapath length [25]. There are 24 metapaths of length 1, 242 metapaths of length 2, and 1,939 metapaths of length 3.

## Gamma-hurdle distribution

### Empirical DWPC p-values

We [calculate](#) an empirical  $p$ -value for special cases where the gamma-hurdle model cannot be applied. These cases include when the observed DWPC is zero or when the null DWPC distribution is all zeroes or has only a single distinct nonzero value. The empirical  $p$ -value ( $p_{\text{empiric}}$ ) equals the proportion of null DWPCs  $\geq$  the observed DWPC.

Since we don’t store all null DWPC values, we apply the following criteria to calculate  $p_{\text{empiric}}$  from summary statistics:

1. When the observed DWPC = 0 (no paths of the specified metapath existed between the source and target node),  $p_{\text{empiric}} = 1$ .
2. When all null DWPCs are zero but the observed DWPC is positive,  $p_{\text{empiric}} = 0$ .

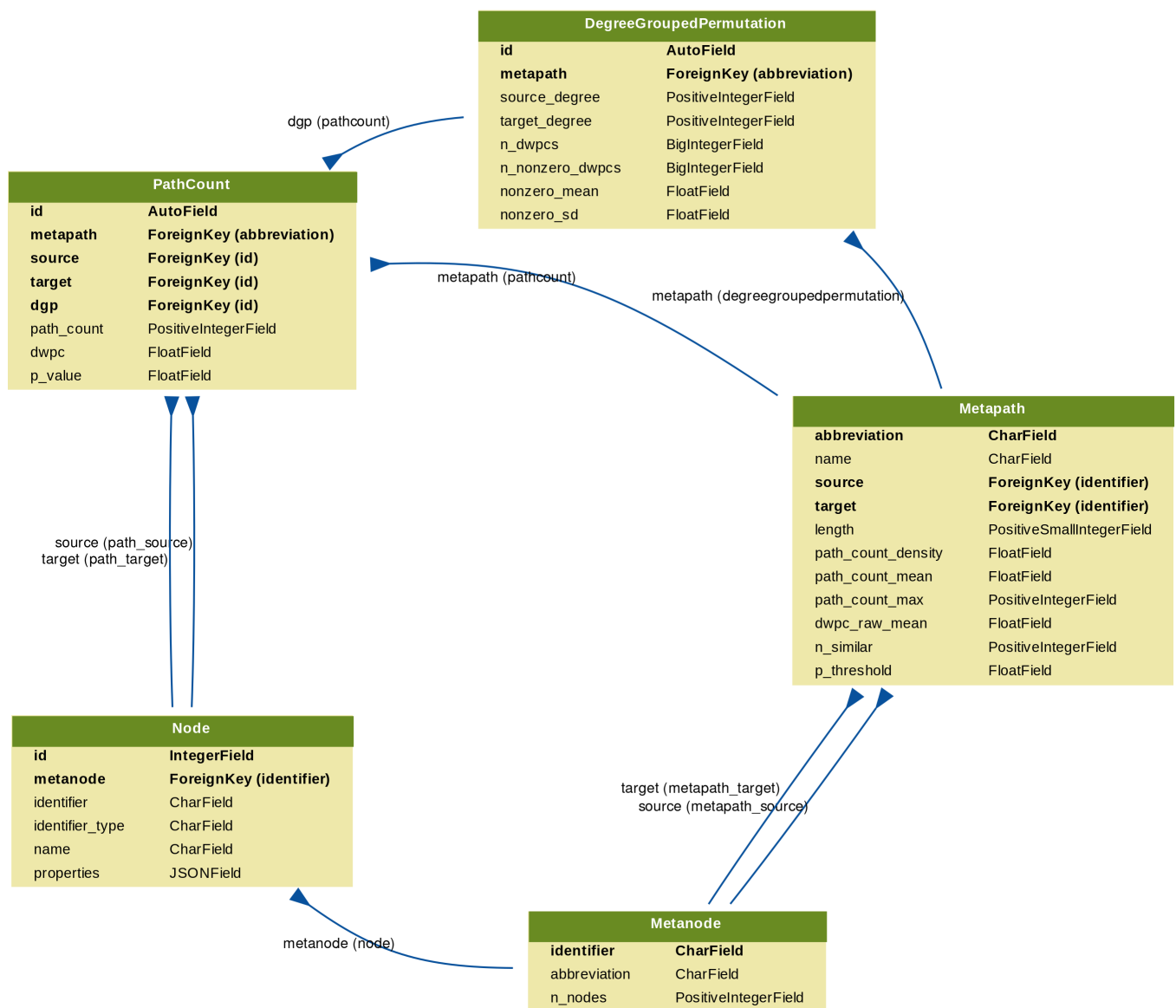
- When all nonzero null DWPCs have the same positive value (standard deviation = 0),  $p_{empiric} = 0$  if the observed DWPC > the null DWPC else  $p_{empiric} =$  proportion of nonzero null DWPCs.

## Prioritizing metapaths for database storage

### Rest API & backend

We created a backend application using Python's Django web framework. The source code is available in the [connectivity-search-backend](#) repository. The primary role of the backend is manage a relational database and provide an API for requesting data.

We define the database schema [using](#) Django's object-relational mapping framework (Figure 4). We [import](#) the data into a PostgreSQL database. Populating the database for all 2,205 metapaths up to length 3 was a prolonged operation, [taking](#) over 3 days. The majority of the time is spent populating the [DegreeGroupedPermutation](#) (37,905,389 rows) and [PathCount](#) (174,986,768 rows) tables.



**Figure 4: Schema for the connectivity search backend relational database models.** Each Django model is represented as a table, whose rows list the model's field names and types. Each model corresponds to a database table. Arrows denote foreign key relationships. The arrow labels indicate the foreign key field name followed by reverse relation names generated by Django (in parentheses).

We host a public API instance at <https://search-api.het.io>. Version 1 of the API exposes several endpoints that are used by the connectivity search frontend including queries for node details ( /v1/node ), node lookup ( /v1/nodes ), metapath information ( /v1/metapaths ), and path information ( /v1/paths ). The endpoints return JSON payloads. Producing results for these queries relies on internal calls to the PostgreSQL relational database as well as the pre-existing Hetionet v1.0 Neo4j graph database. They were designed to power the hetnet connectivity search webapp, but are also available for general research use.

## **Webapp & Frontend**

## **Realtime open science**

## **Software & data availability**



## References

---

### 1. Renaming “heterogeneous networks” to a more concise and catchy term

Daniel Himmelstein, Casey Greene, Sergio Baranzini

*ThinkLab* (2015-08-16) <https://doi.org/f3mn4v>

DOI: [10.15363/thinklab.d104](https://doi.org/10.15363/thinklab.d104)

### 2. Human Disease Ontology 2018 update: classification, content and workflow expansion

Lynn M Schriml, Elvira Mitra, James Munro, Becky Tauber, Mike Schor, Lance Nickle, Victor Felix, Linda Jeng, Cynthia Bearer, Richard Lichenstein, ... Carol Greene

*Nucleic Acids Research* (2019-01-08) <https://doi.org/ggx9wp>

DOI: [10.1093/nar/gky1032](https://doi.org/10.1093/nar/gky1032) · PMID: [30407550](https://pubmed.ncbi.nlm.nih.gov/30407550/) · PMCID: [PMC6323977](https://pubmed.ncbi.nlm.nih.gov/PMC6323977/)

### 3. Unifying disease vocabularies

Daniel Himmelstein, Tong Shu Li

*ThinkLab* (2015-03-30) <https://doi.org/f3mqv5>

DOI: [10.15363/thinklab.d44](https://doi.org/10.15363/thinklab.d44)

### 4. Systematic integration of biomedical knowledge prioritizes drugs for repurposing

Daniel Scott Himmelstein, Antoine Lizee, Christine Hessler, Leo Brueggeman, Sabrina L Chen, Dexter Hadley, Ari Green, Pouya Khankhanian, Sergio E Baranzini

*eLife* (2017-09-22) <https://doi.org/cdfk>

DOI: [10.7554/elife.26726](https://doi.org/10.7554/elife.26726) · PMID: [28936969](https://pubmed.ncbi.nlm.nih.gov/28936969/) · PMCID: [PMC5640425](https://pubmed.ncbi.nlm.nih.gov/PMC5640425/)

### 5. Wikidata as a knowledge graph for the life sciences

Andra Waagmeester, Gregory Stupp, Sebastian Burgstaller-Muehlbacher, Benjamin M Good, Malachi Griffith, Obi L Griffith, Kristina Hanspers, Henning Hermjakob, Toby S Hudson, Kevin Hybiske, ... Andrew I Su

*eLife* (2020-03-17) <https://doi.org/ggqqc6>

DOI: [10.7554/elife.52614](https://doi.org/10.7554/elife.52614) · PMID: [32180547](https://pubmed.ncbi.nlm.nih.gov/32180547/) · PMCID: [PMC7077981](https://pubmed.ncbi.nlm.nih.gov/PMC7077981/)

### 6. SemMedDB: a PubMed-scale repository of biomedical semantic predications

H. Kilicoglu, D. Shin, M. Fiszman, G. Roseblat, T. C. Rindflesch

*Bioinformatics* (2012-10-08) <https://doi.org/f4hp3x>

DOI: [10.1093/bioinformatics/bts591](https://doi.org/10.1093/bioinformatics/bts591) · PMID: [23044550](https://pubmed.ncbi.nlm.nih.gov/23044550/) · PMCID: [PMC3509487](https://pubmed.ncbi.nlm.nih.gov/PMC3509487/)

### 7. Constructing Biomedical Knowledge Graph Based on SemMedDB and Linked Open Data

Qing Cong, Zhiyong Feng, Fang Li, Li Zhang, Guozheng Rao, Cui Tao

*2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)* (2018-12)

<https://doi.org/ggzb26>

DOI: [10.1109/bibm.2018.8621568](https://doi.org/10.1109/bibm.2018.8621568)

### 8. Time-resolved evaluation of compound repositioning predictions on a text-mined knowledge network

Michael Mayers, Tong Shu Li, Núria Queralt-Rosinach, Andrew I. Su

*BMC Bioinformatics* (2019-12-11) <https://doi.org/ggpcsr>

DOI: [10.1186/s12859-019-3297-0](https://doi.org/10.1186/s12859-019-3297-0) · PMID: [31829175](https://pubmed.ncbi.nlm.nih.gov/31829175/) · PMCID: [PMC6907279](https://pubmed.ncbi.nlm.nih.gov/PMC6907279/)

### 9. Announcing PharmacotherapyDB: the Open Catalog of Drug Therapies for Disease

Daniel Himmelstein

*ThinkLab* (2016-03-15) <https://doi.org/f3mqtv>

DOI: [10.15363/thinklab.d182](https://doi.org/10.15363/thinklab.d182)

10. **Our hetnet edge prediction methodology: the modeling framework for Project Rephetio**  
Daniel Himmelstein  
*ThinkLab* (2016-05-04) <https://doi.org/f3qbmj>  
DOI: [10.15363/thinklab.d210](https://doi.org/10.15363/thinklab.d210)
11. **edge2vec: Representation learning using edge semantics for biomedical knowledge discovery**  
Zheng Gao, Gang Fu, Chunping Ouyang, Satoshi Tsutsui, Xiaozhong Liu, Jeremy Yang, Christopher Gessner, Brian Foote, David Wild, Ying Ding, Qi Yu  
*BMC Bioinformatics* (2019-06-10) <https://doi.org/ggpcsq>  
DOI: [10.1186/s12859-019-2914-2](https://doi.org/10.1186/s12859-019-2914-2) · PMID: [31238875](https://pubmed.ncbi.nlm.nih.gov/31238875/) · PMCID: [PMC6593489](https://pubmed.ncbi.nlm.nih.gov/PMC6593489/)
12. **metapath2vec: Scalable Representation Learning for Heterogeneous Networks**  
Yuxiao Dong, Nitesh V. Chawla, Ananthram Swami  
*KDD '17: Proceedings of the 23rd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining* (2017-08) <https://doi.org/gfsgzn>  
DOI: [10.1145/3097983.3098036](https://doi.org/10.1145/3097983.3098036)
13. **HINE: Heterogeneous Information Network Embedding**  
Yuxin Chen, Chenguang Wang  
*Lecture Notes in Computer Science* (2017) <https://doi.org/gg2c7t>  
DOI: [10.1007/978-3-319-55753-3\\_12](https://doi.org/10.1007/978-3-319-55753-3_12)
14. **Discovering Meta-Paths in Large Heterogeneous Information Networks**  
Changping Meng, Reynold Cheng, Silviu Maniu, Pierre Senellart, Wangda Zhang  
*Association for Computing Machinery (ACM)* (2015) <https://doi.org/gg2c7v>  
DOI: [10.1145/2736277.2741123](https://doi.org/10.1145/2736277.2741123)
15. **MetaExp: Interactive Explanation and Exploration of Large Knowledge Graphs**  
Freya Behrens, Fatemeh Aghaei, Emmanuel Müller, Martin Preusse, Nikola Müller, Michael Hunger, Sebastian Bischoff, Pius Ladenburger, Julius Rückin, Laurenz Seidel, ... Davide Mottin  
*WWW '18: Companion Proceedings of the The Web Conference 2018* (2018-04)  
<https://doi.org/gg2c7w>  
DOI: [10.1145/3184558.3186978](https://doi.org/10.1145/3184558.3186978)
16. **Transforming DWPCs for hetnet edge prediction**  
Daniel Himmelstein, Pouya Khankhanian, Antoine Lizée  
*ThinkLab* (2016-04-01) <https://doi.org/f3qbmd>  
DOI: [10.15363/thinklab.d193](https://doi.org/10.15363/thinklab.d193)
17. **Heterogeneous Network Edge Prediction: A Data Integration Approach to Prioritize Disease-Associated Genes**  
Daniel S. Himmelstein, Sergio E. Baranzini  
*PLOS Computational Biology* (2015-07-09) <https://doi.org/98q>  
DOI: [10.1371/journal.pcbi.1004259](https://doi.org/10.1371/journal.pcbi.1004259) · PMID: [26158728](https://pubmed.ncbi.nlm.nih.gov/26158728/) · PMCID: [PMC4497619](https://pubmed.ncbi.nlm.nih.gov/PMC4497619/)
18. **Using the neo4j graph database for hetnets**  
Daniel Himmelstein  
*ThinkLab* (2015-10-02) <https://doi.org/f3mqvk>  
DOI: [10.15363/thinklab.d112](https://doi.org/10.15363/thinklab.d112)
19. **Estimating the complexity of hetnet traversal**  
Daniel Himmelstein, Antoine Lizée

*ThinkLab* (2016-03-22) <https://doi.org/gbr42x>  
DOI: [10.15363/thinklab.d187](https://doi.org/10.15363/thinklab.d187)

**20. Path exclusion conditions**

Daniel Himmelstein

*ThinkLab* (2015-12-08) <https://doi.org/gg2rw2>  
DOI: [10.15363/thinklab.d134](https://doi.org/10.15363/thinklab.d134)

**21. Vagelos Report Summer 2017**

Michael Zietz

*Figshare* (2017) <https://doi.org/gbr3pf>  
DOI: [10.6084/m9.figshare.5346577](https://doi.org/10.6084/m9.figshare.5346577)

**22. Randomization Techniques for Graphs**

Sami Hanhijärvi, Gemma C. Garriga, Kai Puolamäki

*Society for Industrial & Applied Mathematics (SIAM)* (2009-04-30) <https://doi.org/f3mn58>  
DOI: [10.1137/1.9781611972795.67](https://doi.org/10.1137/1.9781611972795.67)

**23. Assessing the effectiveness of our hetnet permutations**

Daniel Himmelstein

*ThinkLab* (2016-02-25) <https://doi.org/f3mqt5>  
DOI: [10.15363/thinklab.d178](https://doi.org/10.15363/thinklab.d178)

**24. Network Edge Prediction: Estimating the prior**

Antoine Lizee, Daniel Himmelstein

*ThinkLab* (2016-04-14) <https://doi.org/f3qbm5>  
DOI: [10.15363/thinklab.d201](https://doi.org/10.15363/thinklab.d201)

**25. Node Connectivity Measurements For Hetionet V1.0 Metapaths**

Daniel Himmelstein, Michael Zietz, Kyle Kloster, Michael Nagle, Blair Sullivan, Casey Greene

*Zenodo* (2018-11-06) <https://doi.org/gg2wr7>  
DOI: [10.5281/zenodo.1435834](https://doi.org/10.5281/zenodo.1435834)