Generating new drug repurposing hypotheses using disease-specific hypergraphs

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The drug development pipeline for a new compound can last 10-20 years and cost over $10 billion. Drug repurposing offers a more time- and cost-effective alternative. Computational approaches based on network graph representations, comprising a mixture of disease nodes and their interactions, have recently yielded new drug repurposing hypotheses, including suitable candidates for COVID-19. However, these interactomes remain aggregate by design and often lack disease specificity. This dilution of information may affect the relevance of drug node embeddings to a particular disease, the resulting drug-disease and drug-drug similarity scores, and therefore our ability to identify new targets or drug synergies. To address this problem, we propose constructing and learning disease-specific hypergraphs in which hyperedges encode biological pathways of various lengths. We use a modified node2vec algorithm to generate pathway embeddings. We evaluate our hypergraph's ability to find repurposing targets for an incurable but prevalent disease, Alzheimer's disease (AD), and compare our ranked-ordered recommendations to those derived from a state-of-the-art knowledge graph, the multiscale interactome. Using our method, we successfully identified 7 promising repurposing candidates for AD that were ranked as unlikely repurposing targets by the multiscale interactome but for which the existing literature provides supporting evidence. Additionally, our drug repositioning suggestions are accompanied by explanations, eliciting plausible biological pathways. In the future, we plan on scaling our proposed method to 800+ diseases, combining single-disease hypergraphs into multi-disease hypergraphs to account for subpopulations with risk factors or encode a given patient's comorbidities to formulate personalized repurposing recommendations.

Keywords: Hypergraphs, Precision Medicine, Drug Repurposing, Disease Specificity

1. Introduction

The development of new drugs can take more than 15 years, from the discovery and pre-clinical phase to review by regulatory agencies.[1] Hence, repurposing drugs already approved by the Food and Drug Administration or European Medicines Agency serves as a convenient alternative since they have already known to be safe in human populations. From an research and development perspective, drug repurposing is a less risky enterprise. Indeed, following compound identification, repositioned drugs would generally hit the market in less than 10 years. Beyond time savings, this strategy brings significant cost savings, potentially reduc-

ing the average pharmaceutical pipeline's budget by over $5 billion compared to traditional drug development. To date, drug repurposing encompasses three main approaches: computational biomedicine,[2] biological experimentation, and their combination, e.g., through systems pharmacology.[3]

Computational approaches are both more time-effective and cost-effective than *in vitro* or *in vivo* biological experiments, which involve high-throughput screening or phenotypic screening based on animal and human models, respectively. Examples of available strategies include signature matching, genome-wide association studies, and the retrospective analysis of real-world clinical information.[4] Their use has been unlocked by the concurrent emergence of technical advances such as biological microarrays and the increase in data accessibility, as illustrated by the rapid growth of electronic health records and biobanks.[5]

Simultaneously, massive genomic databases and cell lines have yielded 20+ high-quality biological and biomedical knowledge graphs (KG) such as SPOKE[?] and PrimeKG[6] and aggregating platforms such as the KG-Hub[7] to ensure that the former can be shared and made interoperable for downstream graph machine learning tasks. Network-based methods for drug repurposing rely on the encoding of interactions between entities (i.e., drugs, diseases, proteins, biological functions) that can be heterogeneous (i.e., inhibition, binding). These representations can help address both predictive (e.g., polypharmacy side effects) and inferential (e.g., reasoning over causal pathways) questions. Prior graph representations such as the multiscale interactome (MSI)[8] have proved useful in identifying known drug repurposing agents and formulating potential candidates.

However, drug repurposing hypotheses output by algorithms or deep learning models deployed on KGs may appear as "black boxes". Yet structural and/or functional explanations are desirable and often necessary to understand the possible mechanisms of action underlying a predicted relationship between an existing drug and a disease – be it beneficial or detrimental. Further, KGs integrating various data sources are rarely disease-specific. Thus, they may result in overall drug similarities that do not hold for the pathology of interest or in spurious correlations.

Contributions. Hypergraphs have seen success in identifying relationships in areas like marketing,[9] finance,[10] and computer vision,[11] so we propose disease-specific hypergraphs as the basis for data-driven drug repurposing. Importantly, hypergraphs allow encoding of relationships among groups of nodes (i.e., hyperedges) rather than pairwise relationships (i.e., edges) only. Here, hyperedges capture known biological pathways. First, we show that the properties of hypergraphs reflect relative disease complexity. Second, we transform disease-specific hypergraphs into weighted graphs where nodes encode biological pathways and weighted edges the number of entities (e.g., gene) that they have in common. We focus on pathways that start with a drug entity and end with the disease entity of interest, irrespective of their length. Using a modified node2vec[12] algorithm, we learn the disease-specific embeddings of each hyperedge. In particular, we use these low-dimensional representations to find original biological pathways that are highly similar to those whose starting entity is a drug currently prescribed to treat the disease or mitigate its progression. Then, we pool the top candidate biological pathways and

analyze the distributions of starting drug entities and middle gene entities to gain a mechanistic understanding of promising drug classes and targets. We illustrate our proposed method in the context of Alzheimer's disease (AD), a multi-factorial disease of aging that still has no cure despite recent progress. We demonstrate that our proposed method outputs candidate biological pathways that are topologically non-obvious, i.e., they do not have any entities in common with pathways involving currently prescribed drugs besides the end disease entity. To validate the utility and complementary of learning disease-specific pathway embeddings, we compare these non-obvious suggestions to those of the MSI and validate our findings by searching the biomedical literature to find supporting evidence. Our comparative analysis and publication search reveals that certain candidates that were highly ranked by our hypergraph-based learning approach for AD drug repurposing (i.e., in the top 10%) and had supporting evidence can be missed by the MSI (i.e., in the bottom 33% across all drugs). Going forward, our proposed framework can be scaled to derive novel drug repurposing hypotheses for each of the 800+ major diseases currently registered (i.e., excluding rare and orphan diseases).

2. Methods

In this section, we describe our proposed approach, which encompasses three main parts: hypergraph construction, pathway/hyperedge representation learning, and comparative performance evaluation against the multiscale interactome.[8]

2.1. *Hypergraph Construction*

We built disease-specific hypergraphs by querying the Hetionet[13] knowledge graph, which comprises 1,522 drugs, 5,734 side effects, and 137 diseases, to extract significant biological pathways connecting each drug present in the KG to the disease of interest. Hetionet is an existing state-of-the-art knowledge graph that incorporates 11 node types (e.g., gene, symptom), allowing for vast heterogeneity in the (node) composition of "metapaths" from a compound to a disease that we sample from to create disease-specific hypergraphs(see Figure 1a). We query the Hetionet to retrieve all paths starting at one of the 1,522 drugs and ending at a disease of choice. These paths are further grouped into metapath categories based on the type and order of nodes present within the path. For example, a metapath group could be "drug-gene1-gene2-disease." We use the direct weighted path count and adjusted p-value defined by Hetionet to quantify the significance of a path relative to its metapath group. We include the top 10% most significant paths within each group to create our induced disease-specific subgraph. We reasoned that selecting only the most significant pathways would help mitigate the resulting number of false positives among drug repurposing candidates. The largest connected component is treated as the subgraph of interest (see Figure 1b); other components are ignored. All existing biological pathways in the resulting subgraph are explicitly unified as hyperedges, creating a disease-specific hypergraph (see Figure 1c). Lastly, we transformed our disease-specific hypergraph into a disease-specific graph where the nodes now correspond to hyperedge/pathways in the hypergraph. Two nodes are connected if they share another/an additional element in their path, besides the start (drug) and end (disease). The edge weight is defined by the number of shared elements $\mathbf{w}$, normalized between 0 and 1 (see Figure 1d).

Note that the maximum edge weight value can differ across disease-specific hypergraphs.

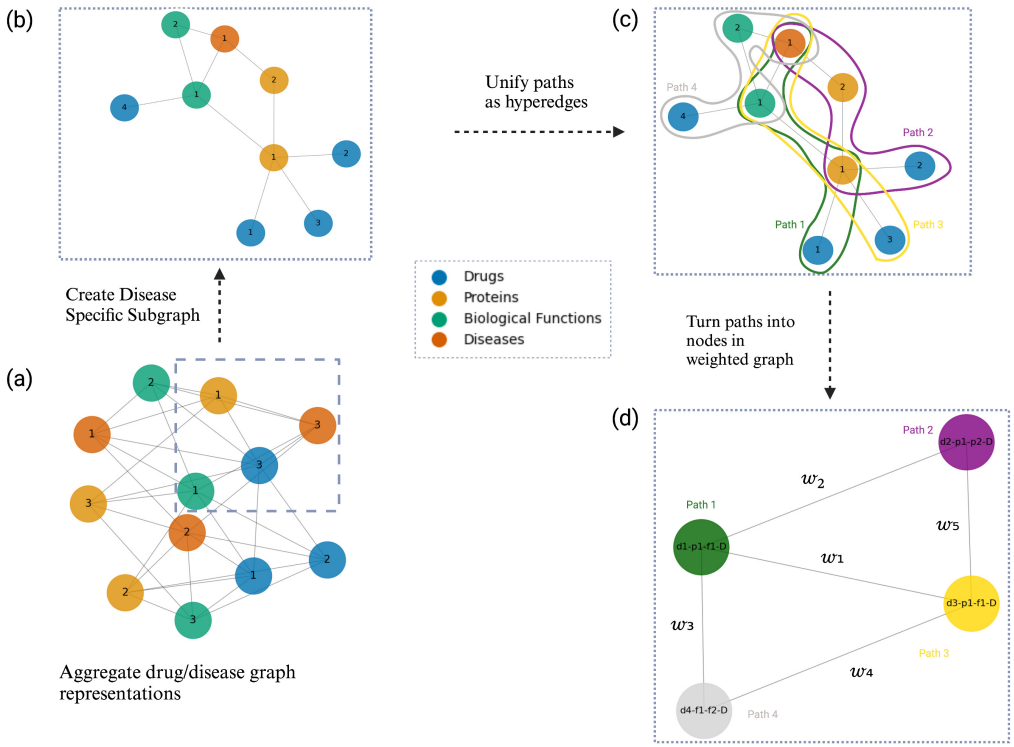


Fig. 1. Pipeline to derive disease-specific hypergraphs from existing KGs and learn contextual embeddings of biological pathways. (a) Full Hetionet graph with nodes of 11 types, including 1,522 drugs, 5,734 side effects, and 137 diseases. (b) Disease-specific subgraph, selecting only the biological pathways whose end node is the disease of interest. Of note, only the top 10% most significant pathways within each metapath group (as defined by their length and structure, e.g., drug-gene1-gene2-disease) are retained, based on a path importance score assigned by Hetionet.[13] (c) Disease-specific hypergraph unifying significant paths or hyperedges in a single structure. (d) Disease-specific weighted graph resulting from the transformation of the hypergraph described in (c). Each hyperedge in (c) becomes a node in (d) and nodes in (d) are connected if their corresponding biological pathways in (c) intersect at two elements at least (the disease node and another element). Each edge is assigned a weight,$\mathbf{w}$, corresponding to the number of elements common to the two biological pathways (note: the weight does not include the disease node, which all pathways present in a given disease-specific hypergraph intersect at; the compound node is not included in the weight, as well).

2.2. *Pathway/Hyperedge Representation Learning*

Given a specific disease of interest, our study aimed to identify biological pathways analogous to those associated with drugs currently used to treat it. In particular, we conducted a case study on Alzheimer's disease and considered medications prescribed to alleviate the symptoms and behavioral complications of Alzheimer's Disease (AD). We focused primarily on three compounds: donepezil, memantine, and galantamine,[?,14,15] approved by the FDA in 1996,

2003, and 2001, respectively. Our approach is disease-agnostic and can be extended to other diseases, upon the supply of a list of compounds currently used in clinical practice or previously suggested as repurposing candidates.

Our methodology involved initiating a random walk on the transformed graph delineated in Fig. 1.d., commencing from any of the nodes with a drug currently prescribed as the first element on the biological pathway. We accounted for the presence of weighted edges by sampling neighboring nodes proportionally to the strength of the connection. The random walker began at a selected node, then proceeded iteratively to an adjacent node chosen at random, and repeated this process for a predetermined number of steps. Each random walk was replicated 10 times for every start node in our projected graph, with a walk path length set at 80.

At each step of the random walk, the probability of transition from biological pathway v to biological pathway x is expressed as:

$$P(v_i = x | v_{i-1} = v) = \frac{\text{weight of edge between } v \text{ and } x}{\text{sum of weights of all edges leaving } v} \tag{1}$$

2.2.1. *Skip-Gram Model*

We interpreted the resulting random walks as sentences, utilizing the Word2Vec Skip-Gram model provided by gensim to develop node embeddings for each biological pathway.[12] This model predicts context words (nodes within the same walk) given a target word (a node). Applied to the context of our disease-specific weighted graph, the embeddings of biological pathways learned through this process encapsulate the local neighborhood structure of the nodes and are subsequently used for our pathway similarity search.

The Skip-Gram model's objective is to devise word representations that effectively predict surrounding words in a sentence or document. Formally stated, given a sequence of training words $w_1, w_2, ..., w_T$, the model aims to maximize the average log probability:

$$\frac{1}{T} \sum_{t=1}^{T} \sum_{-k \leq j \leq k, j \neq 0} \log P(w_{t+j} | w_t) \tag{2}$$

where k denotes the size of the training context and T denotes the total number of training words. We guided the model to learn embeddings of 64 dimensions and subsequently used cosine similarity as the metric to quantify the similarity between any two biological pathways.

Our decision to utilize the Skip-Gram algorithm for learning embeddings was driven by our intent to infer semantic contextual relationships among biological pathways, given a specific disease.

We chose the random walk and skip-gram based approach to learn the embeddings to serve as a proof of concept for our hypergraph construction. Skip-gram based methods focus on the semantic relationships between the nodes as well, which we value due to the encoding of that paths into the node names.[16]

Future research will explore the use of PageRank with teleportation for learning another set of embeddings for each biological pathway and disease. We aim to compare the resulting outputs to our current pathway embeddings pairwise and to assess the sensitivity of the

downstream similarity scores. To derive more robust drug repurposing candidates, several embeddings of biological pathways could be combined.

2.3. *Methods for Evaluation*

Our approach to proposing repurposing hypotheses for a given disease of interest relies on identifying the top 10% of pathway embeddings having the highest cosine similarity with pathways initiating from any of the drugs known to mitigate or prevent disease progression and ending at the disease node. While pathways can include a variety of intermediary nodes (e.g., symptom, anatomical object, etc.), we selected exclusively those pathways with one or more gene intermediary nodes linking one of the 1,522 drug candidates to the considered disease. We reasoned that this feature would help focus our hypotheses on biologically plausible pathways and thus facilitate the interpretation of drug repurposing candidate rankings.

The data and methods of the multiscale interactome (MSI) were used as a baseline for comparative evaluation in this study. The MSI consists in a large biological knowledge graph/KG with 1,566 drugs and 841 diseases and a state-of-the-art random walk approach used to formulate repurposing hypotheses.

Each pathway's rank in terms of cosine similarity to a selected relevant pathway was retained for the purpose of contrasting our own repurposing suggestions with those of the MSI.

From the MSI, we derived rankings of the most similar drug pairs based on the cosine similarity of their embeddings. We also established a rank-ordered list of drugs most similar to the disease of interest (e.g., AD), given their embeddings. We compared these MSI-derived rankings with the top 10% of our own suggestions both locally and globally/overall, aiming to uncover any potential blind spots in the MSI that our methodology might successfully highlight. For each pair, we computed the difference in rank. In addition, we calculated the size of overlap for the top 10%.

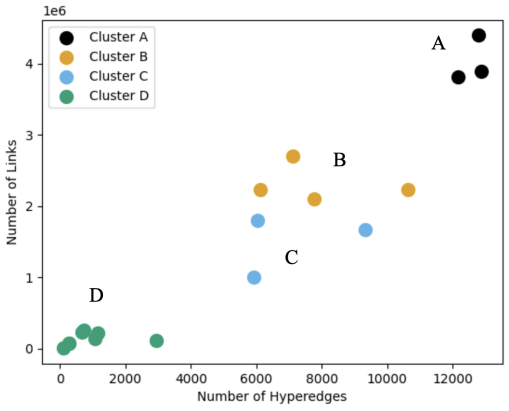
To further validate our methodology and the resulting pathway embeddings, we undertook a deeper analysis of the most disparate/different drug repurposing suggestions. In particular, we searched the biomedical literature for biological and/or clinical evidence about drug repurposing suggestions that either fell within the bottom 33% of the MSI's rank-ordered list ($\geq$1,032) while being in the top 10% of ours or had a high cosine similarity to a pathway linked to a known drug for the considered disease, but without sharing any common intermediary node with it.

3. Results

We conducted experiments on our disease-specific hypergraphs, comprising clustering 18 disease hypergraphs to comprehend known disease complexity, implementing hypergraph representation learning to identify similar drug targets to those in the MSI, and using hypergraph representation learning to pinpoint targets overlooked by the MSI but documented in existing literature.

3.1. *Hypergraph Construction Underlines Known Disease Complexity*

Utilizing our method, we constructed 18 disease-specific hypergraphs, the complete list of which can be found in Figure 2. These 18 hypergraphs were divided into four clusters via the application of the k-means clustering algorithm (k=4). We associated each disease with the quantity of protein nodes it connects within the MSI, employing this as a metric to quantify known disease complexity. Generally, a trend between more complex hypergraphs and increased protein connections to the disease was observed, suggesting that the construction process alone could serve as a means to quantify known disease complexity. This observation, however, brings to light a potential limitation of this method: smaller hypergraphs may likely underperform in hypergraph representation learning. Among the 18 hypergraphs, the diseases in Cluster A (see Figure 2), boast more information in their hypergraphs for us to learn from, prompting us to select one of these diseases for our case study. Alzheimer's Disease (AD) was chosen due to its current prevalence—approximately 6.2 million Americans aged 65 and older are living with AD today, a number which could rise to 13.8 million by 2060.[17] Consequently, the identification of repurposing targets for this disease is of utmost urgency, a task our methodology could directly assist with.



Cluster ID	Diseases Present	Proteins connected in the MSI
A	Alzheimer's Disease (1), Rheumatoid Arthritis (2), ALS (3)	(1) 73 (2) 162 (3) 49
B	Lupus (4), Psoriasis (5), Asthma (6), Hepatitis B (7)	(4) 60 (5) 52 (6) 92 (7) 6
C	Hypertension (8), Type 2 Diabetes (9), Type 1 Diabetes (10),	(8) 151 (9) 78 (10) 9
D	CHD (11), CKD (12), Diabetic Retinopathy (13), Renal Failure (14), Parkinson's Disease (15), AIDS (16), Atrial Fibrillation (17), Vascular Dementia (18)	(11) 15 (12) 39 (13) 13 (14) 13 (15) 39 (16) 1 (17) 34 (18) N/A

Fig. 2. The scatter plot illustrates clusters of diseases based on the attributes of their respective disease-specific hypergraphs, constructed as outlined in sections 1(b-c). Diseases deemed to be of high complexity (for instance, AD) are positioned in the top right corner, a determination made based on their intricate higher-order hypergraph structure. Conversely, diseases deemed to be of lower complexity (such as renal failure) are situated in the bottom left corner. The complexity is assessed by the quantity of currently known biological pathways involved. This higher-order structural information is contrasted with the number of proteins to which each disease is directly connected (that is, one-hop neighbors) within the multiscale interactome[8]

3.2. *Hypergraph Representation Learning Identifies Repurposing Targets in Accordance with the MSI*

Both the MSI and our AD specific hypergraph shared a 50% overlap in drug categories for their repurposing suggestions: psycholeptics, psychoanaleptics, and drugs used in diabetes management, all of which are supported to have repurposing targets to AD in the literature.[18,19] The MSI also brought attention to drugs acting on the renin-angiotensin system, sex hormones, and other nervous system drugs, thereby grouping together common co-morbidity targets for AD treatment.[20–23] In contrast, our AD-specific hypergraph focused more on antineoplastic agents, cardiac therapy, and ophthalmologicals, each of which has been associated with AD in the literature, as well[?,24,25] .

It is important to note the discrepancy in the number of paths considered when generating Figure 3(a)-(g) and Figure 3(h)-(n). The former, involving 926 paths, includes all paths in the AD hypergraph that start with a drug in the top 10% cosine similarity to AD in the MSI. Conversely, the latter, with 574 paths, only encompasses the top 10% of pathways that exhibit the highest cosine similarity to paths initiating from donepezil, memantine, or galantamine.

These findings underscore the efficacy of our disease-specific hypergraph approach in targeting drugs with pathways highly similar to those of known pertinent drugs when identifying potential candidates for repurposing. Moreover, these outcomes provide initial validation to our hypergraph representation learning method, which will be further discussed in the following subsection.

3.3. *Hypergraph Representation Learning Identifies Drug Repurposing Targets Discounted from the MSI but Present in Literature*

Hypergraph representation learning suggested 7 drug repurposing targets out of its top 30 (23%) that the MSI discounted (rank of ≥ 1032 in either column (2) or (3) of Table 1). The 7 drugs were eplerenone (diruetic), fosphenytoin (cardiac therapy), exemestane (endocrine therapy), eperisone (muscle relaxants), protriptyline (psychoanaleptics), ethotoin (antiepileptics), and pentamidine (antiprotozoals). 4 out of 7 (eplernone, pentamidine, exemestane, and protriptyline) of these have literature supporting their potential efficacy against AD. For the remaining 3 out of 7 (eperisone, ethotoin, and fosphenytoin), we explored tangential literature to evaluate the suggestion and/or looked upon the path that this suggestion headed in hopes of understanding why the prediction was made. Refer to Table 1 for the exhaustive list of the top 30 repurposing suggestions based on pathway similarity to donepezil, memantine, or galantamine in the AD hypergraph.

3.3.1. *Literature Review on 7 Targets Found by Hypegraph Representation Learning but Missed by MSI*

In this section, we delve into the literature that supports our hypotheses for drug repurposing. These drugs were identified as potential repurposing candidates, yet were overlooked by the MSI.

Eplernone has been observed to decrease brain damage, defined by cell death and cortical

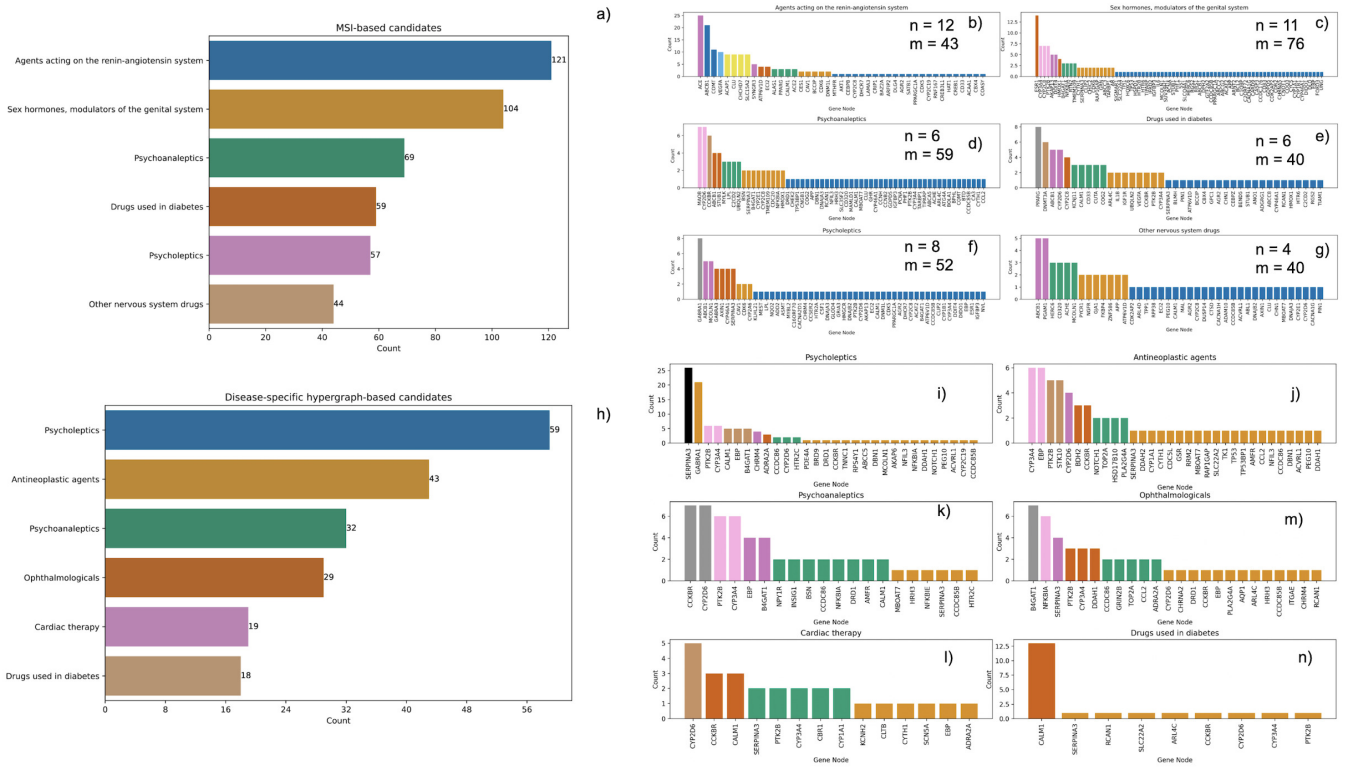


Fig. 3. (a)-(g) illustrate the number of gene targets within the paths of our AD hypergraph, originating from a drug node that ranks within the top 10% in terms of highest cosine similarity to the AD node in the MSI. (h)-(n) depict the number of gene targets in paths within our AD hypergraph that are within the top 10% in similarity to the pathways of donepezil, memantine, and galantamine, only considering paths with gene intermediary nodes. (a) presents the six categories with the most gene targets among the MSI's top 10% suggestions. Conversely, (h) displays the six categories with the most gene targets in the AD hypergraph's top 10% predictions based on similarity to donepezil, memantine, and galantamine. (b)-(g) further break down these top six categories from (a), demonstrating the count of each gene in the top 10% of predicted paths. Similarly, (i)-(n) break down the top six categories from (h), showing the count of each gene within the top 10% of paths similar to those of donepezil, memantine, and galantamine, as determined by cosine similarity. In these graphics, 'n' represents the number of unique drugs within this category, while 'm' signifies the number of unique gene targets in (b)-(g) and (i)-(n).

thinning, in a rat model.[26] Additionally, it is documented that eplernone enhances cognitive function in a mouse model of AD.[27] Another study reinforces these findings, illustrating that eplernone can mitigate cognitive deficits in the hippocampus of spontaneously hypertensive rats.[28] These outcomes coincide with the established correlation between hypertension and dementia/AD.[29] Lastly, an *in silico* pharmacological assessment of eplernone proposed that the drug holds potential in treating AD.[30]

Exemestane exhibits efficacy when AD patients are concurrently dealing with cancer, suggesting that women diagnosed with breast cancer who underwent treatment with tamoxifen or exemestane exhibited fewer instances of AD.[31] A subsequent study characterizes the relationship between AD and cancer, demonstrating that exemestane is proficient at managing

cancer when it co-occurs with AD.[32] Additional research has suggested exemestane as a potential therapeutic for Parkinson's Disease (PD),[33] a neurodegenerative disorder associated with AD.[34]

Protriptyline was found to have the highest inhibitory activity among 140 FDA approved nervous system drugs against the three primary AD targets: AChE, BACE-1, and Aβ aggregation.[35,36] A study using an AD rat model concluded that protriptyline reduces oxidative damage and improves spatial memory in AD mice.[37]

Pentamidine, in a mouse model of AD, was found to inhibit Aβ-induced gliosis and neuroinflammation in AD mice.[38] However, to our knowledge, this is the only publication endorsing its use in alleviating AD, likely because pentamidine is unable to cross the blood-brain barrier. However, recent developments in nose-to-brain methods could surmount this obstacle.[39]

Ethotoin (antiepileptic), to our knowledge, doesn't have explicit literature connecting it to AD. There is, however, a study that warns that antiepileptics could escalate stroke risk in AD patients.[40] This elucidates a current limitation of our approach: we currently do not differentiate between positive and negative drug pathways to a disease.

Fosphenytoin's affect on AD is not specifically discussed in the literature. However, it is a prodrug of phenytoin,[41] which inhibits hippocampal tissue degradation and consequently the progression of AD.[42]

Eperisone lacks direct literature linking it to AD, to the best of our knowledge. When examining the pathway, starting at eperisone and ending at AD that was suggested to have a high similarity to galantamine (see Table 1) in our hypergraph, we find: Eperisone-Triporlidine-CYP2D6-AD. This pathway shows that eperisone was connected to AD by way of similarity to triporlidine. Triporlidine has been observed to enhance NREM sleep in AD patients.[43]

4. Conclusion and Future Directions

Our disease-specific hypergraphs have proven useful for clustering diseases based on their known complexity, identifying potential drug repurposing targets alongside existing methods, and discovering promising repurposing targets overlooked by state-of-the-art methods. We found that the disease hypergraphs formed four clear groups when comparing the number of hyperedges to the number of links between these hyperedges (see Figure 2). Additionally, in Figure 2, we see more complex hypergraphs correlated with more known disease complexity, which we assessed by counting the protein-disease connections in the multiscale interaction.

We also demonstrated the value of this method in generating drug repurposing suggestions for Alzheimer's disease (AD). We saw a significant overlap with the suggestions from the multiscale interaction when looking at the top 10% of suggestions from both methods, especially among drug categories with the highest number of gene targets in the pathways.

Among our top 30 repurposing suggestions for AD, ranked by pathway cosine similarity, we focused on pathways with gene intermediary nodes, hoping to keep our results grounded in biological relevance. Each suggestion comes with the drug pathway that supports its potential use in treating AD (see Table 1 for the full list).

Additionally, our method also identified promising repurposing pathways for AD that the multiscale interaction overlooked. In fact, 7 out of our top 30 suggestions ranked in the

Table 1. This table presents the top 30 pathways - specifically, the 10 most similar pathways per each drug that originate from donepezil, galantamine, or memantine and culminate at AD. Only pathways commencing at one of these three drugs and incorporating exclusively gene intermediaries were considered as queried paths. Column (1) denotes the ranking of these queried paths based on their cosine similarity to the pathway of the drug under investigation. Column (2) provides the rank of the cosine similarity between the starting node of these queried paths and the AD node within the MSI. Column (3) exhibits the rank of the cosine similarity between the starting node of these queried paths and the starting node of the investigated pathway within the MSI.

Queried Paths	Top 30 Closest Paths	Cosine Similarity	(1)	(2)	(3)
Donepezil–ARL4C–RCAN1–Alzheime...	Gliclazide–ARL4C–RCAN1–Alzheim...	0.998504	1	123	945
Donepezil–ARL4C–RCAN1–Alzheime...	Dexfenfluramine–ARL4C–RCAN1–Al...	0.998491	2	915	115
Donepezil–NFIL3–DBN1–Alzheimer...	Amcinonide–NFIL3–DBN1–Alzheime...	0.998409	1	620	630
Donepezil–NFKBIA–B4GAT1–Alzhei...	Rimexolone–NFKBIA–B4GAT1–Alzhe...	0.998569	1	620	750
Donepezil–NFKBIA–B4GAT1–Alzhei...	Testosterone Propionate–NFKBIA...	0.998527	2	620	830
Donepezil–NFKBIA–B4GAT1–Alzhei...	Medroxyprogesterone Acetate–NF...	0.998501	3	93	343
Donepezil–NFKBIA–B4GAT1–Alzhei...	Methyltestosterone–NFKBIA–B4GA...	0.998212	4	101	561
Donepezil–NFKBIA–B4GAT1–Alzhei...	Pentamidine–B4GAT1–Alzheimer's...	0.998146	5	1091	1410
Donepezil–NFKBIA–B4GAT1–Alzhei...	Methylprednisolone–NFKBIA–B4GA...	0.998073	6	544	630
Donepezil–NFKBIA–B4GAT1–Alzhei...	Fluocinolone Acetonide–NFKBIA–...	0.997991	7	544	630
Galantamine–CYP2D6–CCKBR–Alzhe...	Eperisone–Triprolidine–CYP2D6–...	0.989089	1	1350	1354
Galantamine–CYP2D6–CCKBR–Alzhe...	Enzalutamide–Bicalutamide–CYP2...	0.987268	2	620	603
Galantamine–CYP2D6–CCKBR–Alzhe...	Methylnaltrexone–CYP2D6–CCKBR–...	0.987103	3	759	203
Galantamine–CYP2D6–CCKBR–Alzhe...	Ranitidine–CYP2D6–CCKBR–Alzhei...	0.986098	4	21	20
Galantamine–CYP2D6–CCKBR–Alzhe...	Acebutolol–CYP2D6–CCKBR–Alzhei...	0.986035	5	846	972
Galantamine–CYP2D6–CCKBR–Alzhe...	Chlordiazepoxide–CYP2D6–CCKBR–...	0.985522	6	620	93
Galantamine–CYP2D6–CCKBR–Alzhe...	TetraBSNazine–CYP2D6–CCKBR–Alz...	0.985514	7	544	131
Galantamine–MBOAT7–BSN–Alzheim...	Alfacalcidol–MBOAT7–BSN–Alzhei...	0.997171	1	497	552
Galantamine–MBOAT7–BSN–Alzheim...	Protriptyline–MBOAT7–BSN–Alzhe...	0.99693	2	1035	510
Galantamine–MBOAT7–BSN–Alzheim...	Ethotoin–MBOAT7–BSN–Alzheimer'...	0.995548	3	1035	1041
Memantine–GRIN1–PTK2B–Alzheime...	Desoximetasone–PTK2B–Alzheimer...	0.999134	1	372	291
Memantine–GRIN1–PTK2B–Alzheime...	Telithromycin–CYP3A4–PTK2B–Alz...	0.999018	2	123	877
Memantine–GRIN1–PTK2B–Alzheime...	SIMEPREVIR–CYP3A4–PTK2B–Alzhei...	0.998872	3	351	954
Memantine–GRIN1–PTK2B–Alzheime...	Riluzole–PTK2B–Alzheimer's dis...	0.998854	4	759	621
Memantine–GRIN1–PTK2B–Alzheime...	Eplerenone–CYP3A4–AMFR–Alzheim...	0.998814	5	1490	877
Memantine–GRIN1–PTK2B–Alzheime...	Fosphenytoin–CYP3A4–PTK2B–Alzh...	0.998777	6	1431	1177
Memantine–NFKBIA–B4GAT1–Alzhei...	Colchicine–NFKBIA–B4GAT1–Alzhe...	0.998943	2	544	561
Memantine–NFKBIA–B4GAT1–Alzhei...	Exemestane–NFKBIA–B4GAT1–Alzhe...	0.998885	3	1490	1540
Memantine–NFKBIA–B4GAT1–Alzhei...	Potassium Chloride–SLC12A2–B4G...	0.99878	4	846	495
Memantine–NFKBIA–B4GAT1–Alzhei...	Medroxyprogesterone Acetate–NF...	0.998764	5	93	621

lower third of the multiscale interaction's suggestions. We found supporting evidence for these suggestions in the scientific literature, both from studies that directly tested the drugs and from related research.

Looking ahead, we plan to enhance this method in several ways. We aim to refine our hypergraph construction by merging disease hypergraphs of co-occurring diseases such as AD, Type 2 Diabetes, and Hypertension. We'll explore ways to improve our pathway embeddings and, crucially, we'll look beyond the literature review to other forms of validation, including evidence from electronic health records and experimental studies.

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