Modeling Path Importance for Effective Alzheimer's Disease Drug Repurposing

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Recently, drug repurposing has emerged as an effective and resource-efficient paradigm for AD drug discovery. Among various methods for drug repurposing, network-based methods have shown promising results as they are capable of leveraging complex networks that integrate multiple interaction types, such as protein-protein interactions, to more effectively identify candidate drugs. However, existing approaches typically assume paths of the same length in the network have equal importance in identifying the therapeutic effect of drugs. Other domains have found that same length paths do not necessarily have the same importance. Thus, relying on this assumption may be deleterious to drug repurposing attempts. In this work, we propose MPI (Modeling Path Importance), a novel network-based method for AD drug repurposing. MPI is unique in that it prioritizes important paths via learned node embeddings, which can effectively capture a network's rich structural information. Thus, leveraging learned embeddings allows MPI to effectively differentiate the importance among paths. We evaluate MPI against a commonly used baseline method that identifies anti-AD drug candidates primarily based on the shortest paths between drugs and AD in the network. We observe that among the top-50 ranked drugs, MPI prioritizes 20.0% more drugs with anti-AD evidence compared to the baseline. Finally, Cox proportional-hazard models produced from insurance claims data aid us in identifying the use of etodolac, nicotine, and BBB-crossing ACE-INHs as having a reduced risk of AD, suggesting such drugs may be viable candidates for repurposing and should be explored further in future studies.

Keywords: Alzheimer's Disease; Drug Repurposing; Machine Learning.

1. Introduction

Alzheimer's Disease, denoted AD, is a progressive neurodegenerative disorder that accounts for 60%-70% of dementia cases and affects more than 50 million people worldwide today.[1,2] Given the large number of affected individuals and AD's life-threatening nature,[3] extensive resources have been dedicated to developing AD-modifying drugs. Since 2003, inefficacy or

toxicity has accounted for a 95+% failure rate among candidates evaluated for AD treatment.[4,5] Furthermore, none of the current US Food and Drug Administration (FDA)-approved AD drugs are curative; they only slow disease progression. Because of the immense resources required to conduct clinical trials,[6] the numerous failed clinical trials have necessitated the development of a more resource-efficient method for AD drug discovery. In the last decade, the identification of new therapeutic indications for existing FDA-approved drugs, referred to as drug repurposing,[7] has emerged as an effective and resource-efficient paradigm for drug discovery.[8] This is an attractive option as the toxicity, pharmacokinetics, and pharmacodynamics of FDA-approved drugs have already been thoroughly investigated by previous clinical trials.[7,9]

Recently, the curation of comprehensive drug databases has enabled the development of computational methods for AD drug repurposing.[10–14] Among all the methods, network-based methods have shown promising results and emerged as a popular approach.[13,15,16] Network-based methods utilize comprehensive protein-protein, drug-target, and AD-protein interactions to effectively reveal potential therapeutic effects of drugs on AD. Though promising, existing methods[13] measure the therapeutic effects of drugs on AD primarily using count and length of the paths connecting drug nodes and the AD node in the network. Paths of the same length are considered equivalently effective at identifying the therapeutic effect of drugs by these methods. However, in other domains, paths of the same length have been shown to exhibit substantially different levels of importance.[17,18] As such, assuming equal length paths have equal importance could be detrimental to effective drug repurposing for AD.

In this work, we propose a novel method to conduct drug repurposing for AD, MPI (Modeling Path Importance), to address this limitation. Similar to existing methods,[13,14] MPI leverages the interactions between drugs and AD via proteins as indications of the potential therapeutic effects of drugs on AD. Based on the interactions, MPI introduces a scoring function to score and rank drugs for their anti-AD effectiveness. MPI is unique in that it learns node embeddings[19] and prioritizes important paths via these learned embeddings. Recent work[20] has shown that the learned node embeddings can effectively capture the rich structure information within a network. Thus, scoring paths using node embeddings allows MPI to utilize the network structure information to better prioritize paths for effective AD drug repurposing. Specifically, in this study, MPI leverages DeepWalk,[21] a widely used network learning approach, to generate node embeddings. Edges are scored using a normalized dot product between the learned node embeddings; paths and drugs are scored by multiplying individual edge scores. Note that because MPI serves as a general framework, other network learning approaches, such as Node2Vec[20] and graph neural networks,[22] could also be easily incorporated to generate node embeddings.

In this study, we construct a network to conduct drug repurposing for AD by combining protein-protein interactions (PPIs), drug-target interactions (DTIs), and AD-protein interactions (APIs) from multiple data sources. To investigate the effectiveness of MPI, we compare MPI against a commonly utilized network-based drug repurposing method for AD,[13,23] denoted as BSL, using our network. Our experimental results demonstrate that among the top-50 ranked drugs, MPI prioritizes 20% more drugs with anti-AD evidence compared to BSL. We examine published literature and analyze insurance claims meta data to evaluate the evidence of anti-AD

activity among MPI's top prioritized candidates. The results of our evaluation find consensus between published experimental results and our own analysis for a few drug candidates. Notably, angiotensin converting enzyme inhibitors (ACE-INHs) represent a class of drugs that should be further explored for their anti-AD properties. Moreover, other drugs, such as nicotine, that enhance the brains response to acetylcholine and reduce cholinergic atrophy should be examined as well. Conversely, we find that, relative to other evaluated drugs, long-term use of trihexyphenidyl increases the risk of AD. This was corroborated by previously published *in vivo* experiments.[24] Finally, we find etodolac to confer the lowest risk of developing AD among all cyclooxygenase inhibitors (COX-INHs) in our network. Altogether, these findings suggest that MPI may be a viable option with respect to identifying repurposing candidates to treat AD.

2. Materials and Methods

2.1. *Network construction*

PPIs, DTIs and APIs have shown utility for AD drug repurposing.[13] As such, we construct our network using these interactions. Below, we describe our process for compiling the PPIs, DTIs and APIs used to construct our network from public data sources. In total, our network has 327,924, 2,854, and 230 edges corresponding to PPIs, DTIs, and APIs. These edges connect one AD node, 18,527 protein nodes, and 386 drug nodes.

2.1.1. *Protein-protein interactions (PPIs)*

Following Chen et al.,[13] we include a comprehensive list of human PPIs consisting of 327,924 interactions. This list aggregates a total of 21 bioinformatics and systems biology databases with combinations of five types of experimental evidence. We refer the audience of interest to Chen et al.[13] for a detailed description of the databases.

2.1.2. *Drug-target interactions (DTIs)*

We assemble drug-target interactions and bioactivity data from 4 commonly used databases (each downloaded in November 2022): the ChEMBL database[25] (v31), the binding database,[26] the therapeutic target database,[27] and the IUPHAR/BPS guide to pharmacology database.[28] We retain the drug-target interactions that satisfy the following inclusion criteria: 1) binding affinities, including K_i, K_d, IC_{50}, or EC_{50}, must be less than or equal to 10 μM; 2) protein targets and their respective proteins must have a unique UniProt[29] accession number; 3) protein targets must be marked as reviewed in the UniProt database; 4) protein targets must be present in *homo sapiens*.

Additionally, we retain drugs for which we have sufficient sample size to conduct quantitative analysis using MarketScan[30] insurance claims meta data (see Section 2.4). Specifically, included drugs have at least 100 patients with their first dose at least 2 years prior to an AD diagnosis (dx). Additionally, these drugs must have at least 15 patients who eventually received an AD dx. Applying these filters yielded 2,854 edges connecting 386 FDA-approved drugs to 548 protein targets.

2.1.3. AD-*protein interactions (APIs)*

The AD-associated proteins included in the network were identified from multiple sources. 54 β-amyloid-related proteins and 27 tauopathy-related proteins were obtained from Cheng et al..[13] The authors identified proteins that satisfied at least one of the following criteria: 1) the proteins are validated in large-scale amyloid or tauopathy genome-wide association studies; 2) *in vivo* experimental models exhibit evidence that knockdown or overexpression of the protein leads to AD-like amyloid or tau pathology. We also include 93 unique late-onset AD common risk proteins identified by 7 large-scale genetic studies .[31–37] We further incorporate a set of 118 AD-associated proteins introduced in at least 2 out of the 6 following databases (each was downloaded in November 2022): the online Mendelian inheritance in man database,[38] the comparative toxicogenomics database,[39] the HuGE navigator database,[40] the DisGeNET database[41] (v7.0), the ClinVar database[42] and the Open Targets database[43] (v22.09). In total, our network is comprised of 230 unique, AD-associated proteins. Each of the AD-associated proteins are connected to a single AD node with each edge between a protein and the AD node representing an API in our network.

2.2. *Modeling path importance for* AD *drug repurposing*

In this work, we denote the constructed network as G. Each node in G is denoted as v_i. Specifically, drug nodes, protein nodes and the AD node are v_i^d, v_i^g, and v_i^a , respectively. Note that the index, i, does not apply to the AD node as there are not multiple in our network. Each edge that connects node v_i to node v_j is denoted as e_{ij}. Each path is denoted as p_m, and the set of edges involved in a path is denoted $\mathbb{E}_{p_m}$. Below, we denote matrices, scalars and row vectors using uppercase, lowercase, and bold lowercase letters, respectively.

In MPI, we leveraged DeepWalk,[21] a widely used node embedding approach, to learn embeddings for each node in G. First, for each node v_i in the network, we conduct 256 random walks originating from this node, and terminating once the path length reaches 128. DeepWalk is then trained by sliding a window of length 10 over the generated paths. Nodes within the same window are forced to have similar embeddings following the objective function defined in the original paper.[21] Node embeddings for MPI are produced such that they have 128 dimensions.

After generating node embeddings, we score edge, e_{ij}, using a normalized dot product of the embedding of v_i^x (x=d, g or a) and v_j^y (y=d, g or a) as follows:

$$w_{ij} = \frac{\exp(\mathbf{v}_i^x \mathbf{v}_j^{y\top})}{\sum_{k\in\mathbb{V}} \exp(\mathbf{v}_i^x \mathbf{v}_k^{y\top})}, \tag{1}$$

where w_{ij} is the score of the edge e_{ij}; $\mathbf{v}_i^x$ and $\mathbf{v}_j^y$ is the learned embedding of node v_i^x and v_j^y, respectively; $\exp(\cdot)$ is the exponential function; and $\mathbb{V}$ is the set of all the nodes in the network. Note that, in Equation 1, only one of v_i^x and v_j^y could be the AD node. These edge scores are calculated with node embeddings which implicitly capture the rich structural information within the network. Thus, compared to existing methods, MPI can better leverage a network's structural information for AD drug repurposing. We calculate the score for each

path by multiplying the scores of its individual edges as follows:

$$s_{p_m} = \prod_{e_{ij} \in \mathbb{E}_{p_m}} w_{ij}, \tag{2}$$

where s_{p_m} is the score of the path p_m; and $\mathbb{E}_p$ is the set of all the edges in the path p. The score for each drug (i.e., $s_{v_i^d}$) is then defined as the summation of the scores from all 3-hop or shorter paths that originate from the AD node and terminate at the drug node.

2.3. *Baseline method*

To evaluate the performance of MPI, we compare MPI against a network-based method recently developed by Cheng et al.,[13] denoted as BSL. BSL scores drugs based on the shortest distance between the drug targets and the AD-associated proteins (Section 2.1.3) in the network. Specifically, we denote $\mathbb{T}(i)$ as the set of protein targets associated with a given drug v_i^d, and denote $\mathbb{P}$ as the set of AD-associated proteins. The proximity between these two sets is calculated as the average shortest distance between elements in $\mathbb{T}(i)$ and $\mathbb{P}$ as follows:

$$r(\mathbb{T}(i), \mathbb{P}) = \frac{1}{|\mathbb{T}(i)| + |\mathbb{P}|} \left(\sum_{v_j \in \mathbb{T}(i)} \min_{v_k \in \mathbb{P}} d(v_j, v_k) + \sum_{v_k \in \mathbb{P}} \min_{v_j \in \mathbb{T}(i)} d(v_k, v_j) \right), \tag{3}$$

where $r(\mathbb{T}(i), \mathbb{P})$ is the proximity between these two sets; $|\mathbb{T}(i)|$ and $|\mathbb{P}|$ is the size of $\mathbb{T}(i)$ and $\mathbb{P}$, respectively; and $\min_{v_k \in \mathbb{P}} d(v_j, v_k)$ is the shortest distance between v_j and any elements in $\mathbb{P}$. Subsequently, we conduct a permutation test to assess the statistical significance of the calculated proximity. The resulting z-score from this test is used as the score of drug v_i.[13] In BSL, a lower drug score implies a higher potential for effective AD treatment.

2.4. *Validation using MarketScan database*

We use MarketScan medicare supplemental database from 2012–2021 to evaluate drug impact on AD onset via Cox proportional-hazard models.[30] The MarketScan database includes data for over 8 million unique individuals and is comprised of demographic information, administrative information, diagnoses, procedures, and pharmacy records. International Classification of Disease (ICD)-9/ICD-10 codes denote diagnoses and National Drug Codes (NDCs) record pharmacy claims. We use the ICD-9/ICD-10 codes listed in Supplementary Table S4♠ to define AD and comorbidities, which are included as covariates in Cox proportional-hazard models. We conduct our analysis over 1,632,218 unique individuals who were at least 65 years by 2022 and possessed a minimum of five years insurance enrollment prior of first AD diagnosis. Drugs from our constructed network are mapped to NDC codes by partial matching of generic names from MartketScan redbook. We only include patients who took or started taking a drug at least two years prior to AD diagnosis to mitigate the possibility that patients starting a drug already had AD given that AD is difficult to diagnosis.

♠ Supplementary Tables S3, S4, and S5 and code can be found here: https://github.com/ninglab/MPI

3. Results

3.1. MPI *for* AD *drug repurposing*

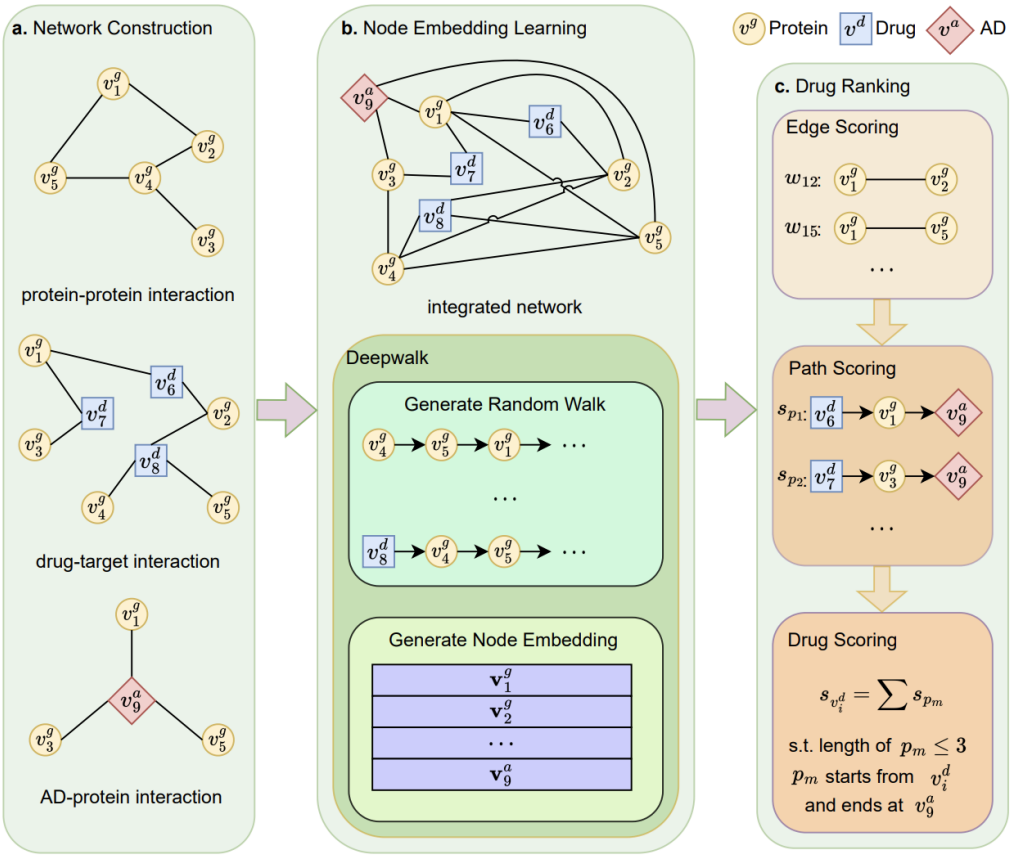


Fig. 1: Figure 1a shows the network construction process in MPI. Figure 1b shows the DeepWalk-based node embedding generation in MPI. Figure 1c shows the edge, path and drug scoring in MPI.

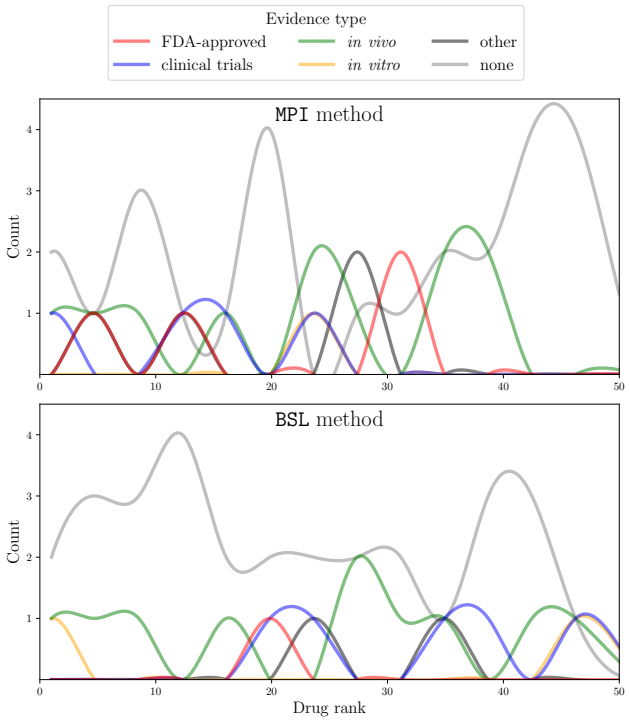
In this study, we curate a network consisting PPIs, DTIs and AGIs and propose a novel network-based method, MPI, for AD drug repurposing. We propose MPI with the following intuitions: 1) proteins that associated with AD are localized in the corresponding disease module within the comprehensive human PPI network; 2) the drug target(s) for a disease may also be targeted for other diseases (e.g., AD) owing to common functional targets and pathways elucidated by PPIs; 3) if a drug node is linked to the AD node through the paths of drug targets and AD-associated proteins in the PPI, the drug may have a treatment effect on AD.

We implement MPI using the following steps: 1) integrate AD-protein interactions, drug-target interactions and protein-protein interactions to generate a comprehensive network (Figure 1a), 2) employ DeepWalk to learn node embeddings which capture the structural information within the network (Figure 1b), and 3) score edges, paths and drugs based on the learned embeddings to leverage the structural information for better AD drug repurposing (Figure 1c). Then we identify plausible treatment candidates from the top-ranked drugs using a literature

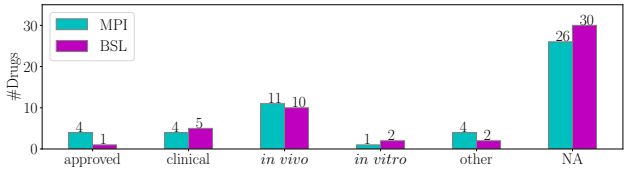
search of the published evidence. We collected 327,924 PPIs from 21 bioinformatics and systems biology databases (Section 2.1.1). We also collected 2,854 DTIs from 4 commonly used databases (Section 2.1.2), and 230 comprehensive APIs from multiple resources (Section 2.1.3). By aggregating all the interactions, we construct a drug-protein-AD network comprised of 386 drug nodes, 18,527 protein nodes, 1 AD node, and 331,008 edges. More details about the network construction are available in Section 2. To the best of our knowledge, MPI is the first method which effectively repurposes drug candidates for AD treatment by prioritizing paths between drug nodes and the AD node using learned node embeddings.

3.2. *Comparing anti-AD evidence of MPI's and BSL's top-50 drugs*

We compare the top-50 drugs prioritized by MPI and BSL to evaluate their capacity for repurposing drugs to treat AD. Specifically, we score and rank all 386 drug nodes in our network using MPI and BSL. The complete rankings are reported in Supplementary Table S3. We then perform a literature search to evaluate the anti-AD evidence of the top-50 ranked drugs for both MPI and BSL. We define anti-AD evidence as any published experimental result(s), which demonstrate a drug either protects against the development of AD or ameliorates aberrant cellular phenotypes caused by AD. We present MPI's and BSL's top-10 drugs and their anti-AD evidence in Table 1 and Table 2, respectively. The complete rankings for the top-50 drugs and their anti-AD evidence is available in Supplementary Tables S1 and S2. Based on the significance of the anti-AD evidence, we categorized drugs into the following 6 types in decreasing order of significance: 1) drugs which are FDA-approved for AD treatment (approved); 2) drugs that have demonstrated anti-AD effects in completed clinical trials or are under investigation in AD clinical trials (clinical); 3) drugs which have demonstrated anti-AD effects in *in vivo* experiments (*in vivo*); 4) drugs which have demonstrated anti-AD effects in *in vitro* experiments (*in vitro*); 5) drugs which show



(a) Distribution of drug rank by evidence type for BSL and MPI methods.



(b) Drug counts for each type of evidence among MPI's and BSL's top-50 drugs.

Fig. 2: Evaluation of drug rank distributions: MPI and BSL.

anti-AD effects in observational studies, cohort studies or analyses in insurance data (other); 6) drugs that either do not have the above 5 types of evidence or have been demonstrated ineffective or damaging for AD (NA). We present the distribution of the top-50 drugs from MPI and BSL over the different types of evidence in Figure 2a and the counts of each evidence type in Figure 2b. In Figure 2a, we observe more drugs with evidence ranked highly by MPI compared to BSL. This is supported by Figure 2b, which confirms that MPI identified more evidential anti-AD drugs compared to BSL in the top-50 ranked drugs. Specifically, among the top-50 ranked drugs, MPI prioritized 24 evidential anti-AD drugs while BSL only prioritized 20 evidential anti-AD drugs, demonstrating an improvement of 20%. Figures 2a and 2b also show MPI outperforms BSL in prioritizing drugs with significant evidence. MPI prioritizes all the 4 FDA-approved anti-AD drugs (e.g., galantamine, rivastigmine, donepezil and memantine) in our network among the top-50. In contrast, BSL prioritizes only a single FDA-approved anti-AD drug (donepezil) among the top-50.

We also observe in Table 1 and Table 2 that MPI is more effective than BSL at prioritizing anti-AD drugs among the very top (top-10) of the ranking list. That is, among the top-10 drugs, 6 drugs from MPI have anti-AD evidence including the FDA-approved AD drug galantamine, while only 4 drugs from BSL are evidential. As presented in Section 2, compared to BSL, MPI learns node embeddings to capture the rich structural information within the network, and leverage the structural information to better identify anti-AD drugs. The superior performance of MPI over BSL demonstrates the effectiveness of leveraging the network structural information to conduct repurposing to identify candidates for AD treatment. We also notice that both MPI and BSL prioritize 17 drugs in concordance within their top-50 drug lists. Among the 17 drugs, 5 drugs demonstrate anti-AD evidence: donepezil is an FDA-approved anti-AD drug; nicotine and rasagiline have clinical anti-AD evidence; and fluvoxamine and fluoxetine have *in vivo* anti-AD evidence. The drugs nicotine, rasagiline, fluvoxamine, and fluoxetine could be promising repurposing candidates. We leave the investigation of these drugs to future research.

3.3. *Identifying repurposing candidates with anti-*AD *activity*

In order to identify plausible candidates for repurposing, we produce Cox proportional-hazard models (see Section 2.4) to ascertain whether there is consensus between the MarketScan insurance data and the AD-related evidence we found for top ranked candidates prioritized by MPI. Specifically, we use hazard ratios (HR) to identify whether any evidential drug elicited reduced the risk of AD diagnosis among patients who took the drug compared against those that did not. We present each drug's HR with their significance levels in Supplementary Table S5b; the HR for each drug's covariates (sex, age, and additional common comorbidities) are reported in Supplementary Table S5c-t. A HR below 1 indicates that a drug has a protective effect, while a HR above 1 indicates that a drug has a damaging effect. Figure 3a plots Kaplan-Meier (KM) survival curves. These plots depict a patient's likelihood of being diagnosed with AD following long-term use of either an individual prescribed drug or a drug with a given mechanism of action (MOA). For MOAs, we group highly-prioritized drugs with published evidence of anti-AD activity (see Table 1). Bupropion (HR = 1.04; non-significant) was included as a negative control as clinical trials found the drug had no significant effect on cognition in

Table 1: Top-10 Drugs from MPI

Drug	MOA	Indication	Anti-AD	Evidence
varenicline	AChR-Ag	smoking cessation	N	-
fosinopril	ACE-INH	hypertension	Y	*in vivo*[44]
nicotine	AChR-Ag	smoking cessation	Y	clinical[45]
nizatidine	histamine receptor antagonist	duodenal ulcer disease	N	-
piroxicam	COX-INH	osteoarthritis	Y	other[46,47]
meloxicam	COX-INH	osteoarthritis	Y	*in vivo*[48–50]
galantamine	AChE-INH	Alzheimer's disease	Y	approved
bromfenac	COX-INH	inflammation	N	-
etodolac	COX-INH	osteoarthritis	Y	*in vivo*[51]
pyridostigmine	AChE-INH	myasthenia gravis	N	-

In this table, the column "Drug" shows the identified top-10 ranked drugs; the column "MOA" shows the mechanism of action of each drug; the column "Indication" presents the indication of each drug; the column "Anti-AD " indicates if the drug has evidenced anti-AD effects; and the column "Evidence" presents the type of the evidence. In this table, ACE-INH represents the angiotensin converting enzyme inhibitor; COX-INH represents the cyclooxygenase inhibitor; AChE-INH represents the acetylcholinesterase inhibitor; and AChR-Ag represents the acetylcholine receptor agonist.

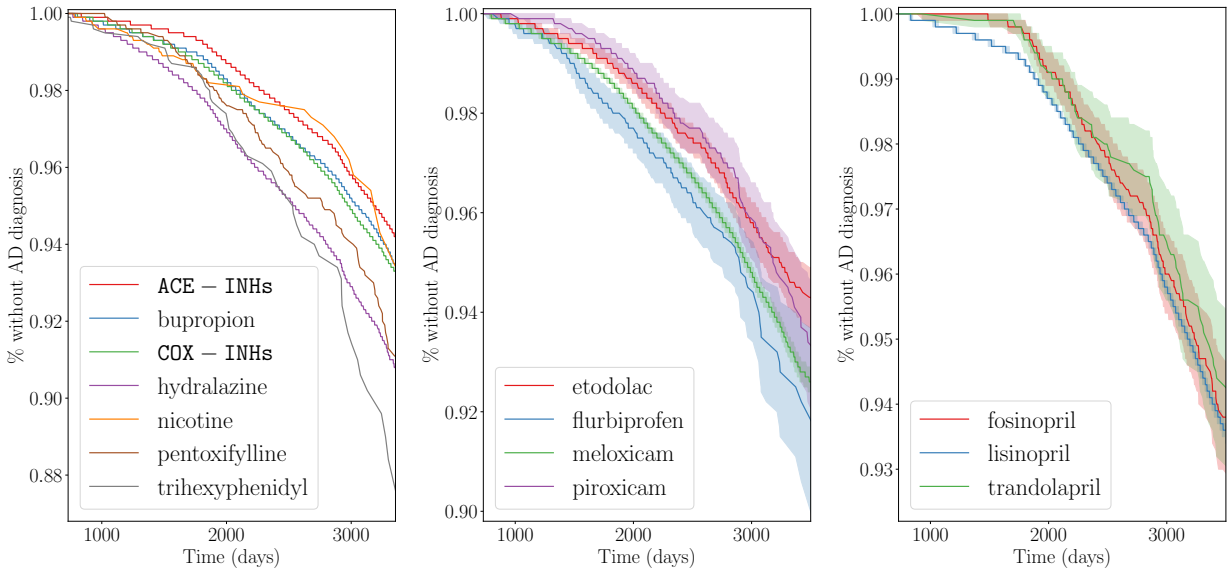
Table 2: Top-10 Drugs from BSL

Drug	MOA	Indication	Anti-AD	Evidence
tetracycline	bacterial 30S ribosomal subunit inhibitor	respiratory tract infections	Y	*in vitro*[52]
selegiline	monoamine oxidase inhibitor	Parkinson's Disease	N	-
ceftriaxone	bacterial cell wall synthesis inhibitor	gonorrhea	Y	*in vivo*[53]
ibuprofen	COX-INH	headache	N	-
levobunolol	adrenergic receptor antagonist	glaucoma	N	-
ketoprofen	COX-INH	rheumatoid arthritis	N	-
carbidopa	aromatic L-amino acid decarboxylase inhibitor	Parkinson's Disease	N	-
sulindac	COX-INH	osteoarthritis	Y	*in vivo*[54]
biotin	vitamin B	supplement	Y	*in vivo*[55]
lansoprazole	ATPase inhibitor	heartburn	N	-

In this table, the column "Drug" shows the identified top-10 ranked drugs; the column "MOA" shows the mechanism of action of each drug; the column "Indication" presents the indication of each drug; the column "Anti-AD " indicates if the drug has evidenced anti-AD effects; and the column "Evidence" presents the type of the evidence. In this table, ACE-INH represents the angiotensin converting enzyme inhibitor; COX-INH represents the cyclooxygenase inhibitor; AChE-INH represents the acetylcholinesterase inhibitor; and AChR-Ag represents the acetylcholine receptor agonist.

AD patients.[56] Trihexyphenydil (HR = 1.71; $\alpha < 0.001$) was included as a positive control for damaging effects due to the evidence documented in Supplementary Table S1. The COX-INHs group includes the following drugs: piroxicam, meloxicam, etodolac, and flurbiprofen. The

ACE-INHs group includes the following drugs: fosinopril, trandolapril, and lisinopril. Note that we only include blood brain barrier (BBB) crossing ACE-INHs in this group as non-BBB-crossing ACE-INHs have exhibited very limited effects on AD.[57] We also include time-to-event analysis for 4 of BSL's top prioritized drugs (See Supplementary Figure S1). Unlike MPI, we observe only one of BSL's drugs (sulindac) with reduced time-to-event compared to bupropion; however, this difference is not significant.



(a) Drugs and MOAs with published anti-AD evidence

(b) COX-INHs. Shaded regions represent 95% confidence intervals.

(c) ACE-INHs. Shaded regions represent 95% confidence intervals.

Fig. 3: Unadjusted Kaplan−Meier plots for cox proportional-hazard models

3.4. *Analyzing the MOAs of* MPI*'s top-50 drugs*

To identify groups of drugs whose anti-AD properties should be further examined and explored, we examine the top-50 drugs prioritized by MPI for any common MOAs. We find that COX-INHs and ACE-INHs are the most common MOAs prioritized by MPI. Both COX-INHs and ACE-INHs have published evidence of anti-AD activity. That said, experimental results suggest that long-term administration of COX-INHs may only have protective properties, reducing the risk of AD onset.[46] Moreover, meloxicam (HR = 0.86; $\alpha < 0.05$), has even shown therapeutic potential, reversing cognitive decline via inhibition of neuronal apoptosis.[48,49] However, in Figure 3a, we observe that COX-INHs as a class do not yield reduced risk of AD compared to the negative control. That said, we find etodolac significantly reduces the risk of AD (HR = 0.78; $\alpha < 0.001$) compared to other COX-INHs, including flurbiprofen (HR = 0.95; non-significant) (Figure 3b). This suggests that only certain COX-INHs, such as etodolac, may elicit protective effects against AD onset. Importantly, this may be a result of differences in target as etodolac targets *COX2*, while flurbiprofen targets *COX1*. On the other hand, ACE-INHs were found to also protect against AD onset in Figure 3a. Specifically, we evaluate only ACE-INHs that cross the blood brain barrier (BBB) as previous insurance claims metadata analyses have indicated those that

do not cross the BBB have no effect on AD.[57] To see if any of the BBB crossing ACE-INHs have a greater protective effect that others, we produce a KM plot for fosinopril, lisinopril, and trandolapril (Figure 3c). Unlike for COX-INHs, ACE-INHs do not elicit any significant by-drug difference in AD onset as illustrated in Figure 3c. While MPI prioritized four BBB crossing (BBBx) and four non-BBBx ACE-INHs in the top-50, the BBBx ACE-INHs had a lower average rank compared to the non-BBBx ACE-INHs (15 and 19, respectively).

Another important distinction between COX-INHs and ACE-INHs is that ACE-INHs have been shown to have some ameliorative potential; whereas, COX-INHs have only shown protective effects. In fact, fosninpril and lisinopril (ranked 2^{nd} and 24^{th} by MPI, respectively) was found to reduce cognitive decline in animal models of AD.[44,58] In Figure 3a, we find that BBBx ACE-INHs consistently exhibit decreased risk of AD relative to our negative control drug, bupropion. Additionally, there does not appear to be a significant difference between any of the BBBx ACE-INHs with respect to their protection against AD, indicating that they are possibly all viable candidates for repurposing. This is in agreement with other published evidence that has identified BBBx ACE-INHs as having protective effect on AD development. Interestingly, MPI prioritized 133.6% more COX-INHs and 700.9% more ACE-INHs than BSL in the top-50 from all such drugs in our network. MPI's ability to prioritize more drugs from MOAs with known anti-AD activity suggests that it may be a more viable option when identifying candidates for drug repurposing.

MPI also highly prioritizes drugs that increase the brain's response to acetylcholine, either by reducing its degradation (acetylcholinesterase inhibitors, AChE-INHs) or by stimulating its receptors (acetylcholine receptor agonists, AChR-Ags). This is important as acetylcholine's (ACh) synaptic bioavailability is an important contributor to AD progression. That is, there is evidence that cholenergic atrophy and ACh deficiency is linked with cognitive decline in AD patients.[59] Moveover, many of the current FDA-approved drugs indicated to slow AD progression target this mechanism of disease progression via AChE-INHs (e.g., donepezil, rivastigmine, and galantamine). AChR-Ags, also enhances ACh signaling. Such drugs, such as nicotine, accomplish this by increasing the response of ACh receptors located on the post-synaptic neuron. Interestingly, nicotine, was found to significantly improve cognition in patients with mild cognitive impairment, which is a precursor to AD.[45] We also find long-term nicotine use to have a protective effect ($\texttt{HR} = 0.532;\ \alpha < 0.001$), with respect to AD onset. In Figure 3a, we observe similar risk of developing AD to ACE-INHs after six to seven years. Conversely, we find evidence that long-term use of trihexyphenidyl, which reduces the activity of ACh receptors, is associated with AD-like neurodegeneration in rats.[24] This is corroborated by Figure 3a, where we observe the highest risk of AD elicited by trihexyphenidyl. More than eight years on trihexyphenidyl was associated with a substantial increase in the risk of AD relative to the other drugs evaluated in Figure 3a. These findings confirm that ACh signaling is closely linked with AD progression. As such, exploring other drugs and drug classes which either increase ACh synaptic bioavailability or enhance neuronal response to ACh should be further examined for anti-AD activity.

4. Discussion

In this work, we propose a novel network-based, AD-specific drug repurposing approach called MPI. MPI improves upon prior network-based methods by leveraging node embeddings learned via DeepWalk to prioritize AD-associated paths. Moreover, the use of learned embeddings allows MPI to more effectively capture a network's rich topology than previous approaches, such as BSL. In a direct comparison, we find that 20% more of MPI's highly prioritized drug candidates (top-50) have published anti-AD evidence compared to BSL's highly prioritized drug candidates. In addition to evidence in literature, we leverage insurance claims data to produce Cox proportional-hazard models. Among all the drugs we evaluate, these models identified BBBx ACE-INHs as having the lowest risk of AD. Similarly, etodolac was found to have the lowest risk of AD among the four COX-INHs we evaluated (Figure 3b), indicating that this drug in particular may have protective effect despite the class as a whole not exhibiting a significantly reduced risk of AD compared to our negative control (Figure 3a). Additionally, MPI highly prioritizes drugs that target the cholinergic system. Each of the approved AD drugs in our dataset that are also AChE-INHs are prioritized in the top-50 by MPI. MPI also highly prioritizes nicotine, an AChR-Ags. This prioritization is supported by both literature and our Cox models, which suggest nicotine is associated with reduced risk of AD. Altogether, the results presented in this work highlight etodolac, nicotine, and ACE-INHs as viable candidates for repurposing to treat AD and, as such, deserve further examination in future studies.

Despite its promising results, MPI exhibits a few limitations. The PPI network we construct is a simplification of molecular pathways. Like many other network-based approaches, MPI does not consider loops nor the directionality of PPI as these can be difficult for models to learn. In our context, this means that highly ranked candidates are only likely to be in close proximity to AD-related genes. To improve drug prioritization, models must be capable of identifying drugs that are both upstream of and in close proximity to these AD-related genes. In future studies, we will leverage directed interactions either by hard coding them or learning them. One way directionality might be learned is through the use of multi-omics data. Examining how changes to genomic and epigenomic profiles affect gene expression could facilitate learning where genes are in pathways. Furthermore, by leveraging multi-omics data, we may be able to provide more personalized drug recommendations.

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Modeling Path Importance for Effective Alzheimer's Disease Drug Repurposing (Supplementary Materials)

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S1. The Top-50 Drugs Identified by MPI and BSL

Table S1: Top-50 Drugs from MPI

Drug	MOA	Indication	Anti-AD	Evidence
varenicline	AChR-Ag	smoking cessation	N	-
fosinopril	ACE-INH	hypertension	Y	*in vivo*[1]
nicotine	AChR-Ag	smoking cessation	Y	clinical[2]
nizatidine	histamine receptor antagonist	duodenal ulcer disease	N	-
piroxicam	COX-INH	osteoarthritis	Y	other[3,4]
meloxicam	COX-INH	osteoarthritis	Y	*in vivo*[5–7]
galantamine	AChE-INH	Alzheimer's disease	Y	approved
bromfenac	COX-INH	inflammation	N	-
etodolac	COX-INH	osteoarthritis	Y	*in vivo*[8]
pyridostigmine	AChE-INH	myasthenia gravis	N	-
bupropion	dopamine reuptake inhibitor	depression	N	-
pentoxifylline	phosphodiesterase inhibitor	claudication	N	-
flurbiprofen	COX-INH	rheumatoid arthritis	Y	clinical[9]
zonisamide	sodium channel blocker	seizures	N	-
apixaban	coagulation factor inhibitor	stroke	Y	other[3,4]
rivastigmine	AChE-INH	Alzheimer's disease	Y	approved
ramipril	ACE-INH	hypertension	Y	clinical[10]
linezolid	bacterial 50S ribosomal subunit inhibitor	pneumonia	N	-
trandolapril	ACE-INH	hypertension	Y	*in vivo*[11]
moexipril	ACE-INH	hypertension	N	-
quinapril	ACE-INH	hypertension	N	-

enalapril	ACE-INH	hypertension	N	-
benazepril	ACE-INH	hypertension	N	-
lisinopril	ACE-INH	hypertension	Y	*in vivo*[12]
hydralazine	vasodilator	hypertension	Y	*in vitro*[13]
rasagiline	monoamine oxidase inhibitor	Parkinson's Disease	Y	clinical[14]
ganciclovir	DNA polymerase inhibitor	cytomegalovirus	Y	*in vivo*[15]
naproxen	COX-INH	pain relief	N	-
fluvoxamine	selective serotonin reuptake inhibitor	obsessive compulsive disorder	Y	*in vivo*[16]
dapsone	bacterial antifolate	dermatitis herpetiformis	Y	other[17]
oxaprozin	COX-INH	osteoarthritis	Y	other[3,4]
ranitidine	histamine receptor antagonist	heartburn	N	-
donepezil	AChE-INH	Alzheimer's disease	Y	approved
memantine	glutamate receptor antagonist	Alzheimer's disease	Y	approved
empagliflozin	sodium/glucose cotransporter inhibitor	diabetes mellitus	Y	*in vivo*[18]
canagliflozin	sodium/glucose cotransporter inhibitor	diabetes mellitus	N	-
alogliptin	dipeptidyl peptidase inhibitor	diabetes mellitus	Y	*in vivo*[19,20]
oxiconazole	bacterial cell wall synthesis inhibitor	tinea pedis	N	-
rivaroxaban	coagulation factor inhibitor	stroke	Y	*in vivo*[21]
fluoxetine	selective serotonin reuptake inhibitor	depression	Y	*in vivo*[22]
azelastine	histamine receptor antagonist	conjunctivitis	N	-
sertraline	selective serotonin reuptake inhibitor	depression	N	-
ibuprofen	COX-INH	headache	N	-
labetalol	adrenergic receptor antagonist	hypertension	N	-
duloxetine	norepinephrine reuptake inhibitor	depression	N	-
quinine	hemozoin biocrystallization inhibitor	malaria	N	-
trihexyphenidyl	acetylcholine receptor antagonist	parkinsonism	N	-
ketoprofen	COX-INH	rheumatoid arthritis	N	-
selegiline	monoamine oxidase inhibitor	Parkinson's Disease	N	-
nortriptyline	tricyclic antidepressant	depression	N	-

In this table, the column "Drug" shows the identified top-50 ranked drugs; the column "MOA" shows the mechanism of action of each drug; the column "Indication" presents the indication of each drug; the column "Anti-AD " indicates if the drug has evidenced anti-AD effects; and the column "Evidence" presents the type of the evidence. In this table, ACE-INH represents the angiotensin converting enzyme inhibitor; COX-INH represents the cyclooxygenase inhibitor; AChE-INH represents the acetylcholinesterase inhibitor; and AChR-Ag represents the acetylcholine receptor agonist.

Table S2: Top-50 Drugs from BSL

Drug	MOA	Indication	Anti-AD	Evidence
tetracycline	bacterial 30S ribosomal subunit inhibitor	respiratory tract infections	Y	*in vitro*[23]
selegiline	monoamine oxidase inhibitor	Parkinson's Disease	N	-
ceftriaxone	bacterial cell wall synthesis inhibitor	gonorrhea	Y	*in vivo*[24]
ibuprofen	COX-INH	headache	N	-
levobunolol	adrenergic receptor antagonist	glaucoma	N	-
ketoprofen	COX-INH	rheumatoid arthritis	N	-
carbidopa	aromatic L-amino acid decarboxylase inhibitor	Parkinson's Disease	N	-
sulindac	COX-INH	osteoarthritis	Y	*in vivo*[25]
biotin	vitamin B	supplement	Y	*in vivo*[26]
lansoprazole	ATPase inhibitor	heartburn	N	-
itraconazole	cytochrome P450 inhibitor	onychomycosis	N	-
ketorolac	COX-INH	pain relief	N	-
quinidine	sodium channel blocker	malaria	N	-
terbinafine	fungal squalene epoxidase inhibitor	tinea pedis	N	-
labetalol	adrenergic receptor antagonist	hypertension	N	-
vilazodone	serotonin reuptake inhibitor	depression	N	-
ivermectin	benzodiazepine receptor agonist	gastrointestinal roundworms	N	-
oxiconazole	bacterial cell wall synthesis inhibitor	tinea pedis	N	-
dabigatran	thrombin inhibitor	stroke	Y	*in vivo*[27]
linezolid	bacterial 50S ribosomal subunit inhibitor	pneumonia	N	-
indomethacin	COX-INH	rheumatoid arthritis	Y	clinical[28]
donepezil	AChE-INH	Alzheimer's disease	Y	approved
levodopa	dopamine precursor	Parkinson's Disease	N	-
ketoconazole	sterol demethylase inhibitor	seborrheic dermatitis	N	-
loratadine	histamine receptor antagonist	allergic rhinitis	N	-
lovastatin	HMGCR inhibitor	coronary heart disease	Y	other[29]
triamterene	sodium channel blocker	hypokalemia	Y	clinical[30]
captopril	ACE-INH	hypertension	Y	*in vivo*[31]
naproxen	COX-INH	pain relief	N	-
methyldopa	adrenergic receptor agonist	hypertension	N	-
fluvoxamine	selective serotonin reuptake inhibitor	obsessive compulsive disorder	Y	*in vivo*[16]
zonisamide	sodium channel blocker	seizures	N	-
diflunisal	prostanoid receptor antagonist	rheumatoid arthritis	Y	*in vivo*[32]
sertraline	selective serotonin reuptake inhibitor	depression	N	-
rasagiline	monoamine oxidase inhibitor	Parkinson's Disease	Y	clinical[14]
verapamil	calcium channel blocker	hypertension	Y	*in vivo*[33]
metoclopramide	dopamine receptor antagonist	gastroparesis	N	-

diclofenac	COX-INH	rheumatoid arthritis	Y	other[34]
bupropion	dopamine reuptake inhibitor	depression	N	-
amiloride	sodium channel blocker	hypertension	Y	clinical[30]
vortioxetine	serotonin receptor agonist	depression	N	-
trazodone	adrenergic receptor antagonist	depression	N	-
losartan	angiotensin receptor antagonist	hypertension	N	-
trihexyphenidyl	acetylcholine receptor antagonist	parkinsonism	N	-
fluoxetine	selective serotonin reuptake inhibitor	depression	Y	*in vivo*[22]
azelastine	histamine receptor antagonist	conjunctivitis	N	-
nicotine	AChR-Ag	smoking cessation	Y	clinical[2]
dexamethasone	glucocorticoid receptor agonist	hypercalcemia	Y	*in vivo*[35]
doxazosin	adrenergic receptor antagonist	benign prostatic hyperplasia	Y	*in vitro*[36]
tramadol	centrally-acting opioid agonist	pain management	N	-

These columns have the same meaning as those in Table S1.

S2. BSL Survival Analysis

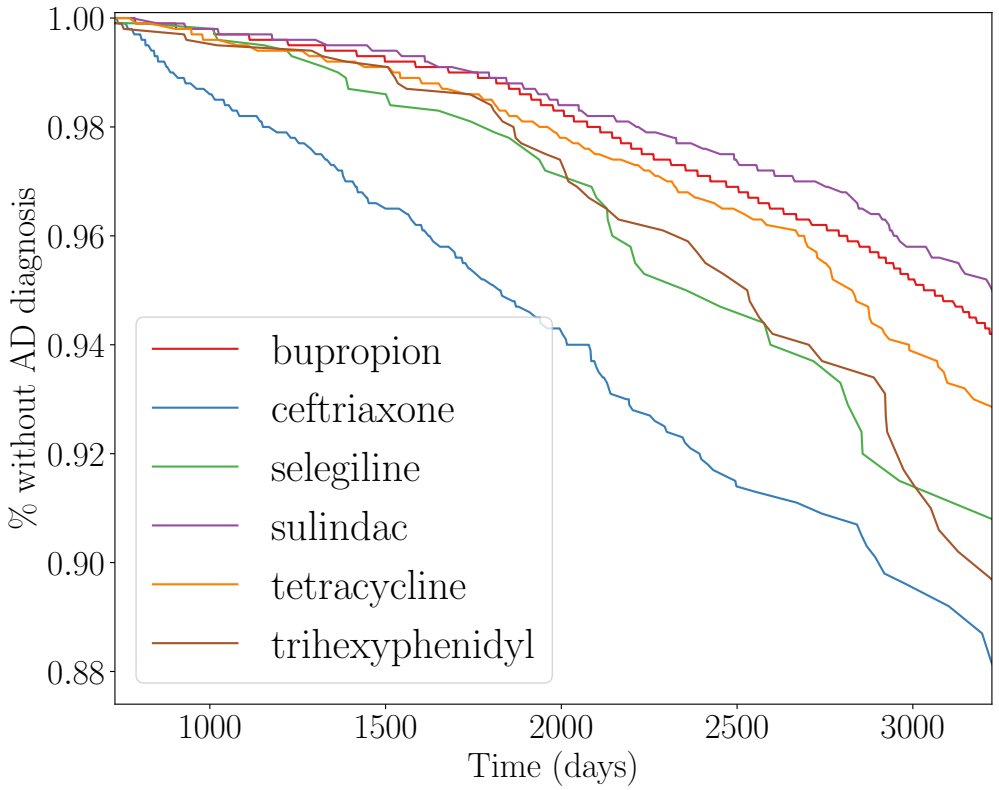

Fig. S1: Unadjusted Kaplan−Meier plots for BSL's top-ranked evidential drugs.

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