COMPUTATIONAL DRUG REPOSITIONING USING KNOWLEDGE GRAPH AND AI

The LNM Institute of Information Technology

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TABLE OF CONTENTS

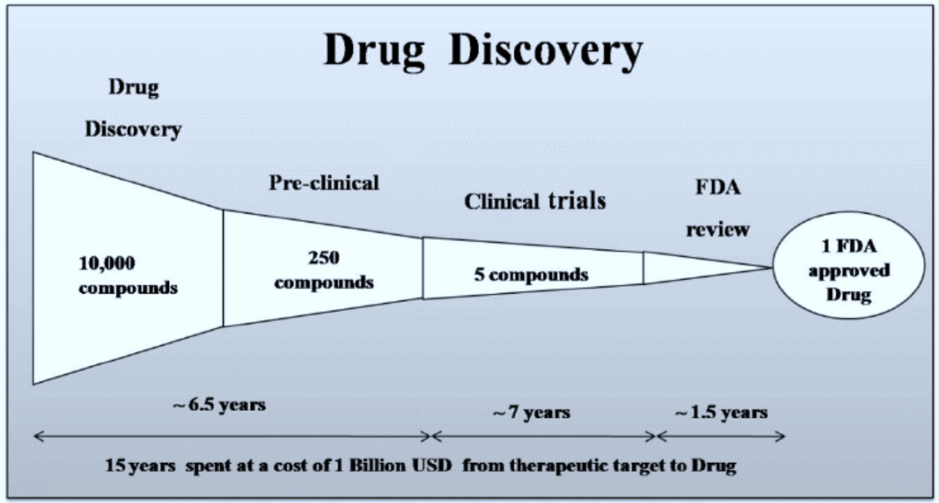
INTRODUCTION

- What is Drug Discovery ?
  - Drug discovery is the process by which new medications are identified and developed.
- What are stages of drug discovery ?
  - Identification of a target
  - Lead compound development
  - Preclinical and clinical testing

Target Discovery → Target Validation → Lead Optimization → Development → Trials

INTRODUCTION

- Limitations of Drug discovery
  - Costly and lengthy process.
  - Four to five main stages.



This is where "Drug Repurposing" is helping

INTRODUCTION

- Areas where Computer Science can contribute?
  - Suggesting candidate drugs.
  - Risk Assessment done by FDA.
  - Dose-Response Analysis can be helped through data science.

- The research paper aims to contribute by identifying existing drugs that could potentially be repurposed for the treatment of other diseases.

INTRODUCTION

- Which tools can be used in perform the above task?
  - Clustering and Classification Algorithms
    - Meticulous analysis and pattern recognition by grouping similar compounds and predicting their efficacy efficiently identify potential drug candidates
    - Undergone extensive research and has reached a saturation point.
  - Regression Analysis
    - Modeling relationships between variables aid in predicting drug effectiveness but not efficient in suggesting candidate drugs.
    - Cornerstone in the realm of drug discovery
  - Deep Learning
    - Forefront of drug discovery research offering immense promise.
    - Our base paper also focuses here.

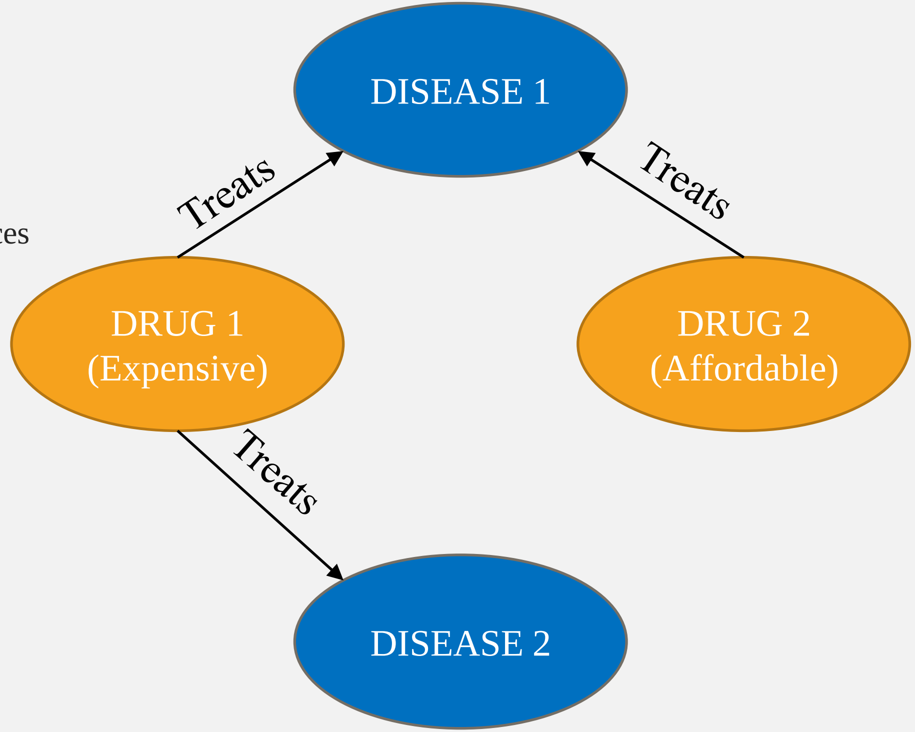
MOTIVATION


Drug repurposing
De novo drug design
Takes 3-12 years
Takes 10-15 years
Has 30-75% success rate
Has < 10% success rate
Costs up to $300 million
Costs up to $2.5 billion

SOME DEFINITIONS

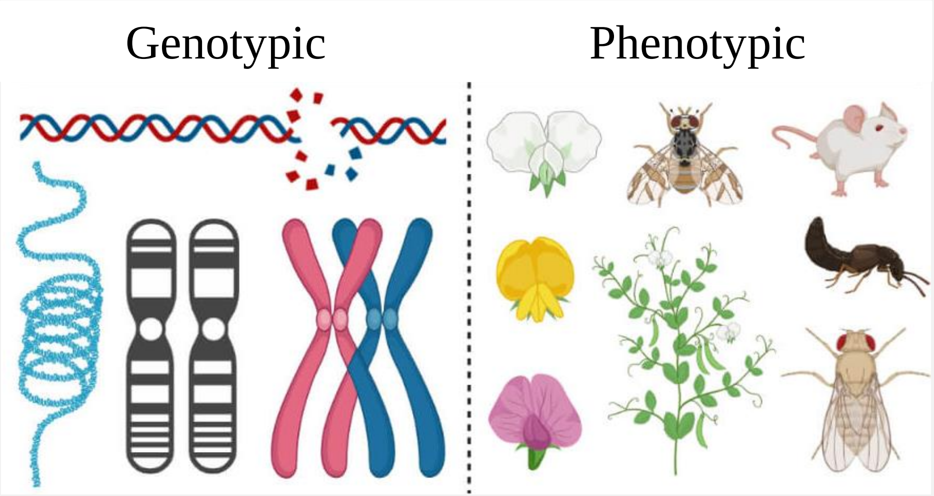
- Knowledge Graph
    - Represents a network of real-world entities
    - Also known as a semantic network
    - Typically made up of datasets from various sources

Our base paper leverages Knowledge Graph technology to facilitate the process of drug repositioning.



SOME DEFINITIONS

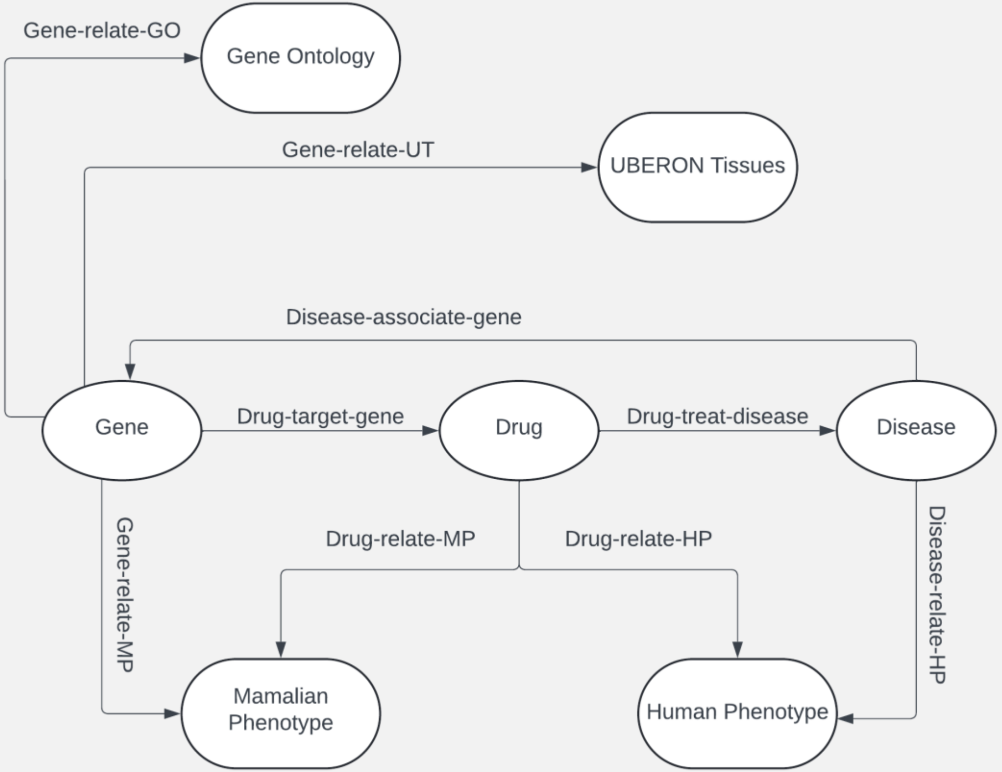
- What is Genotypic and Phenotypic?
  - Genotypic genes are responsible for unique traits or characteristics.
  - Phenotypic genes are responsible for physical appearance or characteristic of an organism.



SOME DEFINITIONS

- Knowledge Graph Construction
  - 61,146 nodes with 7 node types
  - 1,246,726 edges
  - Categorized into 9 semantic relationships
    - 2 from genome-level knowledge databases
    - 1 from text-mined knowledge bases
    - 6 from phenome-level knowledge databases

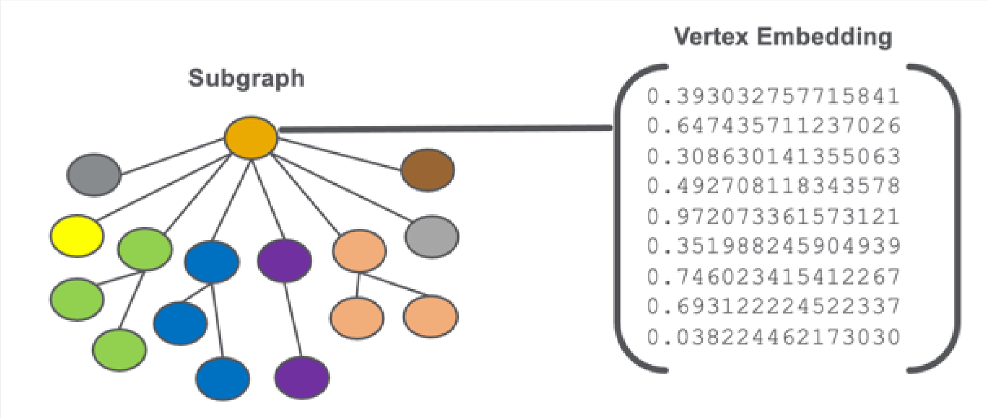
LITERATURE SURVEY



SOME DEFINITIONS

- Traditional machine learning or deep learning algorithms typically operate on fixed-size vectors or matrices.

- How to convert this complex graph into a simpler representation while preserving important information?
    - Graph Embedding - Embeddings encode objects or concepts in a continuous vector space.



SOME DEFINITIONS

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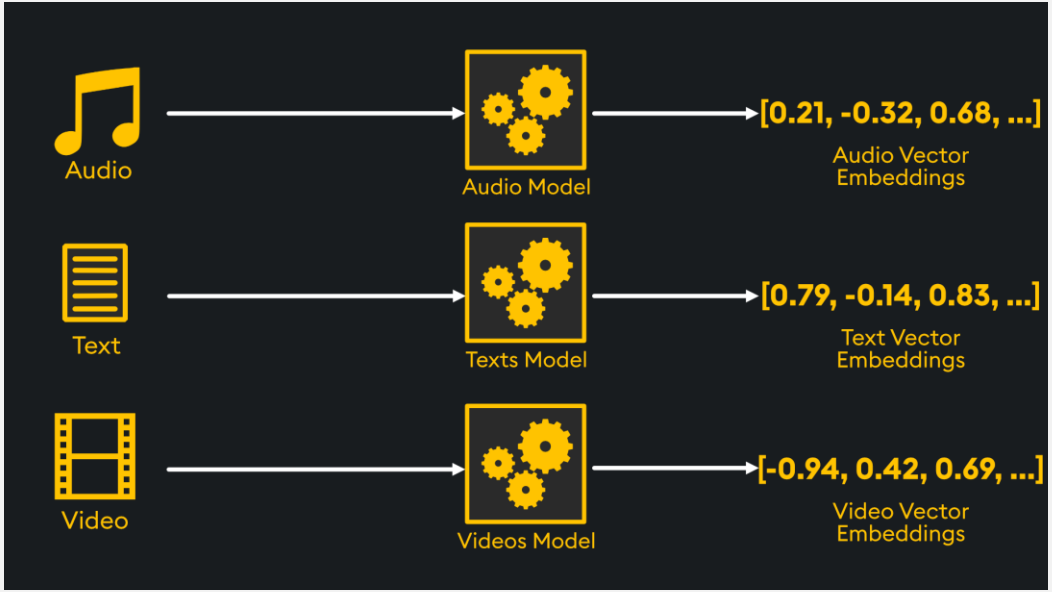
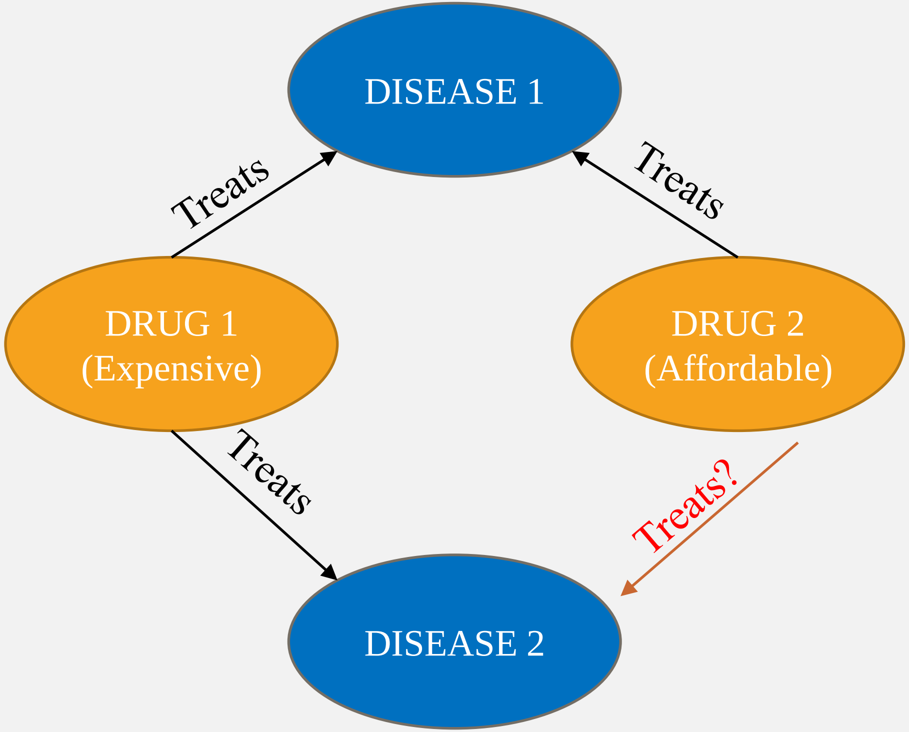
- What do these Numbers Signify?



KNOWLEDGE GRAPH COMPLETION

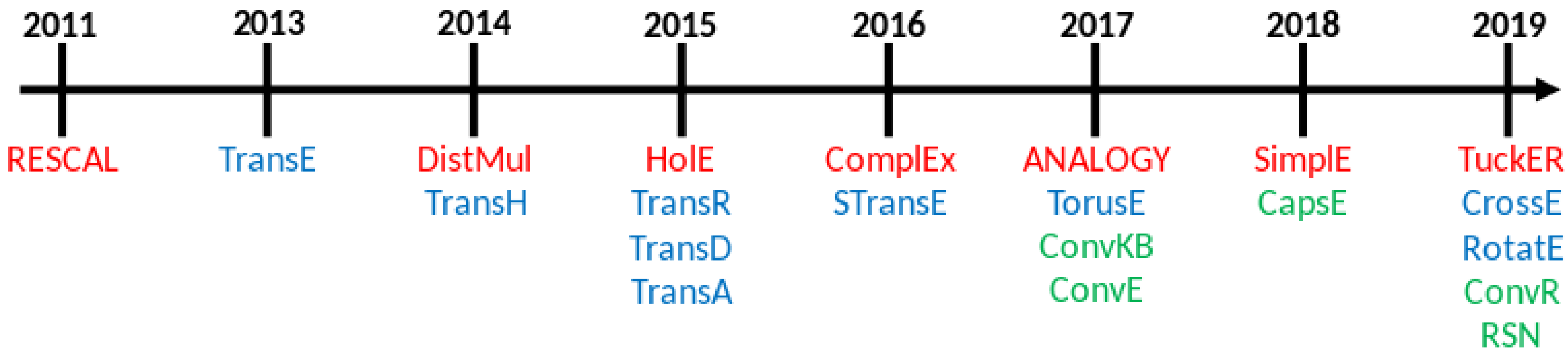
- Given an enormous KG, can we complete the KG?
  - For a given (head, relation), we predict missing tails.
- The graph should contain multiple types of relationships otherwise, you can use the standard link prediction techniques.
- This graph could also include the origin of drugs and the relationship between them.



KG REPRESENTATION

- Edges in KG are represented as triples (h, r, t)
    - head (h) has relation (r) with tail (t)

- Associate entities and relations with shallow embeddings
- Given a triple (h, r, t) the goal is that the embedding of (h, r) should be close to the embedding of t.
    - How to embed (h, r) ?
    - How to define score $f_r\,(h, t)$?
    - Score f_r is high if (h, r, t) exists, else f_r is low



KG EMBEDDING MODELS

LITERATURE SURVEY

- We started looking into pre-existing state of arts model involving different embeddings.
  - TransE
    - Given by- *A. Bordes, N. Usunier, A. Garcia-Duran, J. Weston and O. Yakhnenko.*
  - RotatE
    - Given by- *Z. Sun, Z.H. Deng, J.Y. Nie and J. Tang.*
  - DistMult
    - Given by- *B. Yang, W.T. Yih, X. He, J. Gao and L. Deng*

FOUR RELATION PATTERNS

- Symmetric (Antisymmetric) Relations:
  - $r(h,t) \Rightarrow r(t,h)$ and $r(h,t) \Longrightarrow \neg r(t,h) \quad \forall h,t$
  - Example:
    - Symmetric – Family, Roommate
    - Antisymmetric – Hypernym (colour and red)

- Inverse Relations:
  - $r_1(h,t) \Longrightarrow r_2(t,h)$
  - Example: Advisor and Advisee

FOUR RELATION PATTERNS

- Composition (Transitive) Relations:
  - $r_1(x, y)$ & $r_2(y, z) \Rightarrow r_3(x, z) \quad \forall x, y, z$
  - Example: My mother's husband is my father.

- 1-to-N Relations:
  - $r(h, t_1),\ r(h, t_2),\ \ldots, r(h, t_n)$ are all true.
  - Example: ***r*** is the '*student_of*'

TransE

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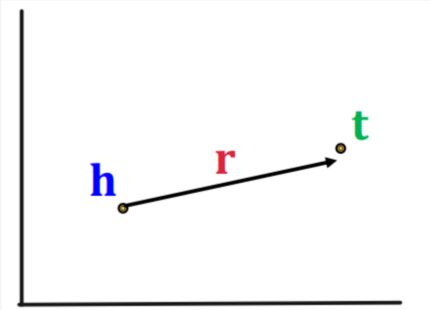
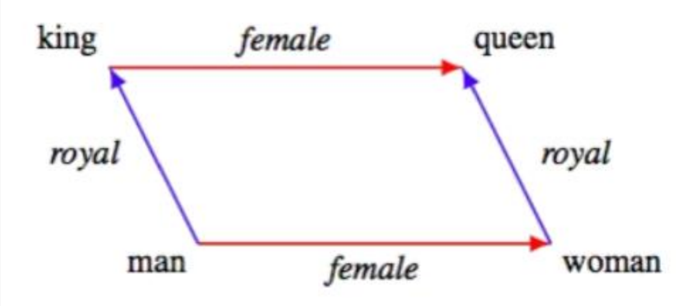
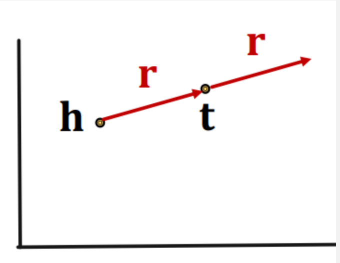
- Translation:
  - For a triple (h, r, t), let $\boldsymbol{h}, \boldsymbol{r}, \boldsymbol{t} \in \mathbf{R}^{\mathbf{d}}$ be embedding vectors.
    - if the given link exists - $\boldsymbol{h} + \boldsymbol{r} \approx \boldsymbol{t}$
    - else $\boldsymbol{h} + \boldsymbol{r} \neq \boldsymbol{t}$



- Entity scoring function: $f_r(h, t) = -|| \, h + r \, - t \, ||$

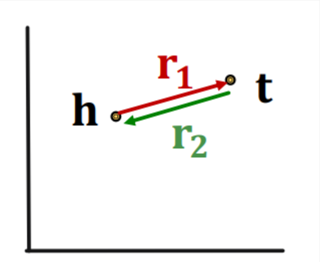


TransE



Antisymmetric:
$r(h,t) \Longrightarrow \neg r(t,h)$

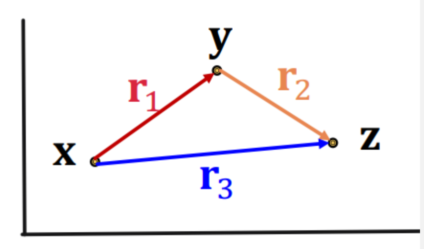
$h + r = t \; but \; t + r \neq h$



Inverse:
$r_1(h,t) \Longrightarrow r_2(t,h)$

$h + r_2 = t$
$and \; we \; can \; set$

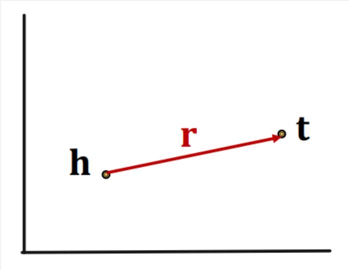
$r_1 = -r_2$



Composition:
$r_1(x,y) \;\&\; r_2(y,z)$
$\Rightarrow r_3(x,z) \quad \forall x,y,z$

$r_1 + r_2 = r_3$

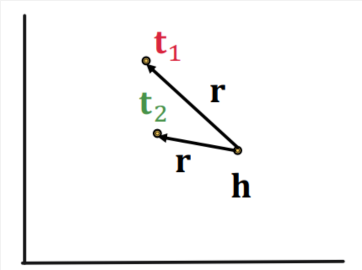
TransE - Limitation



Symmetric:

$r(h,t) \Longrightarrow r(t,h)$

$Only\ if\ r = 0\ and\ h = t$



1-to-N:

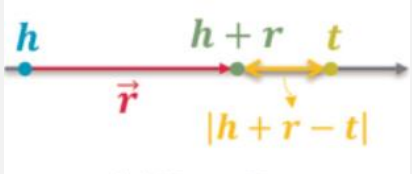
$r(h,t_1), r(h,t_2),\ \ldots, r(h,t_n)$ are all true.

$t_1 = h + r = t_2$

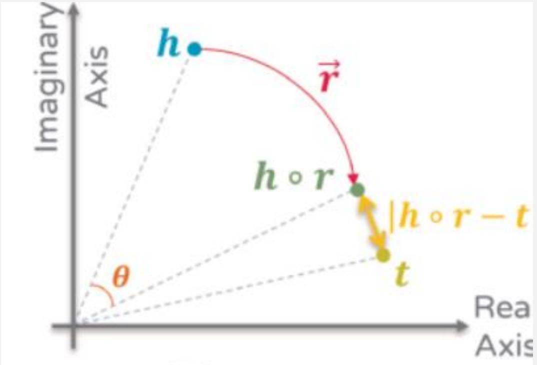
$t_1\ and\ t_2$ will map to the same vector although they are different entities.

RotatE

- Translation:
  - For a triple (h, r, t), let $\boldsymbol{h, r, t} \in \mathbf{R^d}$ be embedding vectors.
    - if the given link exists - $\boldsymbol{h} \circ \boldsymbol{r} \approx \boldsymbol{t}$
    - else $\boldsymbol{h} \circ \boldsymbol{r} \neq \boldsymbol{t}$
    - where '∘' is the Hadamard product on the embeddings.



(a) TransE

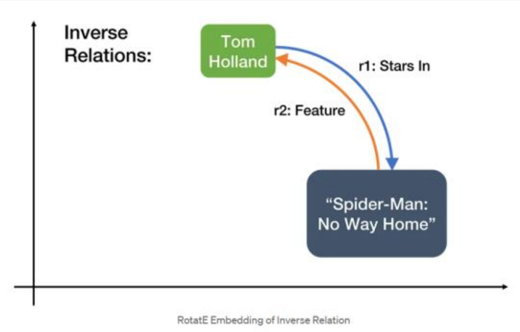


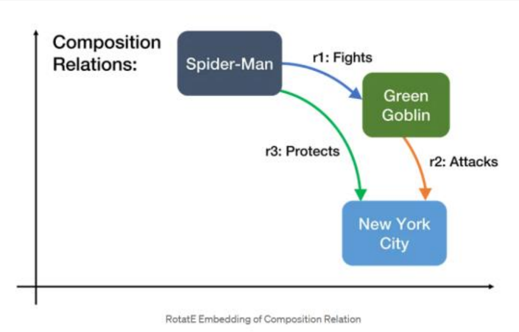
(b) RotatE

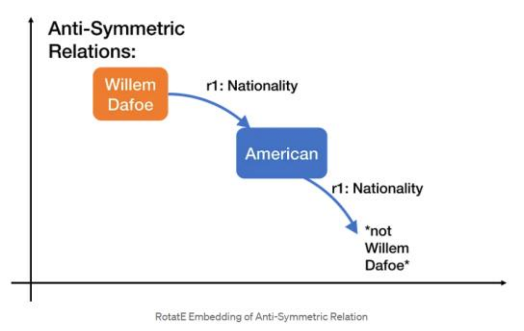
- Entity scoring function: $f_r(h, t) = -||h \circ r \ - t\ ||^2$

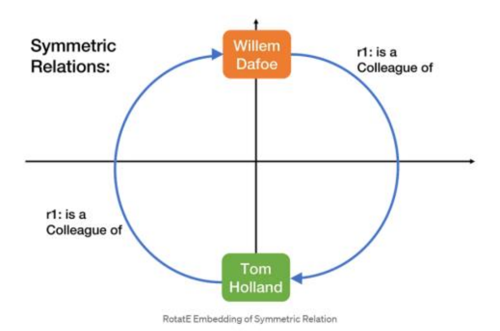
The Hadamard product is a binary operation that takes in two matrices of the same dimensions and returns a matrix of the multiplied corresponding elements.

RotatE



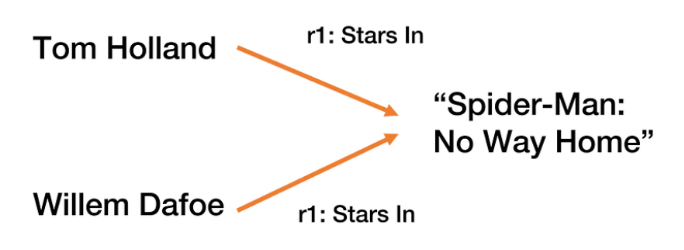




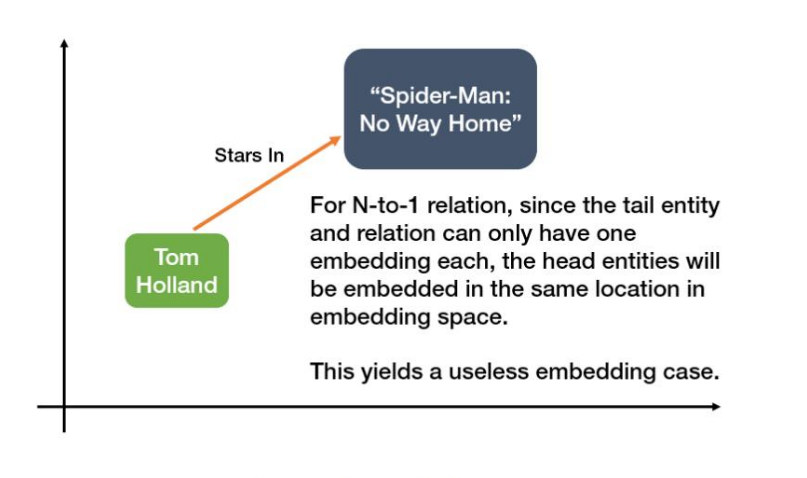


RotatE can model symmetric relations that TransE cannot express! It does so as 180-degree rotations.

RotatE - Limitation



Knowledge Graph with N-to1 Relation



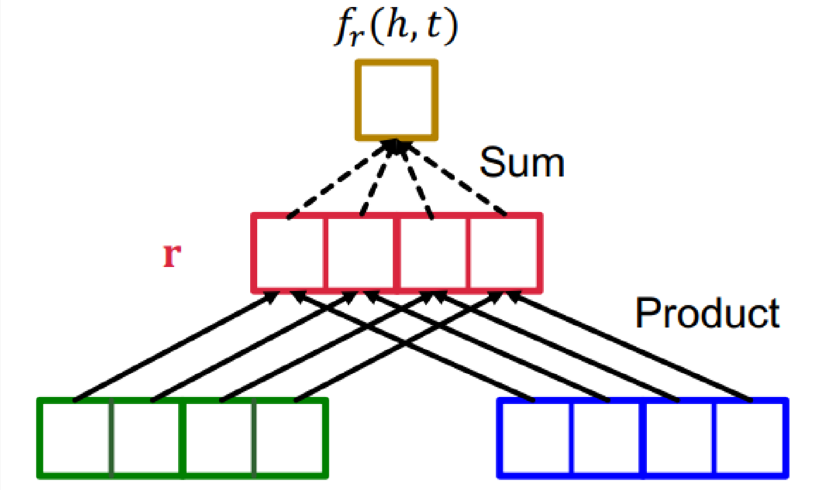
TransE Embedding of N-to-1 Relation

DistMult

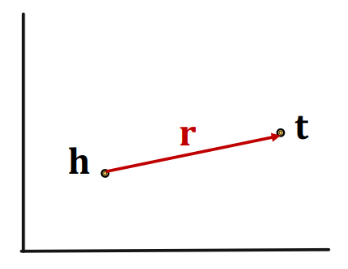
- For a triple (h, r, t), let $\mathbf{h}, \mathbf{r}, \mathbf{t} \in \mathbf{R}^{\mathbf{d}}$ be embedding vectors.

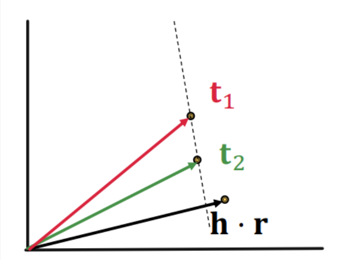
- Score function: $f_r(h,t) = < h, r, t >$
  $= \sum_i \; h_i \,.\, r_i \,.\, t_i$

- Intuition of score function:
  - Cosine similarity between $h \,.\, r \; and \; t$



DistMult





Symmetric:

$r(h,t) \implies r(t,h)$

$$f_r(h,t) = \langle h, r, t \rangle = \sum_i h_i \,.\, r_i \,.\, t_i$$
$$= \langle t, r, h \rangle = f_r(t,h)$$

1-to-N:

$r(h,t_1), r(h,t_2), \ \ldots, r(h,t_n)$ are all true.

$$\langle h, r, t_1 \rangle = \langle h, r, t_2 \rangle$$

DistMult - Limitations

Antisymmetric:
$r(h,t) \Longrightarrow \neg r(t,h)$

$f_r(h,t) = < h, r, t >$
$= \sum_i h_i . r_i . t_i$
$= < t, r, h > = f_r(t,h)$

Inverse:
$r_1(h,t) \Longrightarrow r_2(t,h)$

$< h, r_1, t > = < t, r_2, h >$
$r_1 = r_2$ solves this

But semantically it does not make sense
(advisor is not equal to advisee)

Composition:
$r_1(x,y) \,\&\, r_2(y,z)$
$\Rightarrow r_3(x,z) \quad \forall x,y,z$

Since dot product is commutative, it can distinguish between head and tail entities

Summary – Embedding Models

Model	**Score**	**Symmet.**	**Antisym.**	**Inverse**	**Compos.**	**1-to-N**
TransE	$-\|\| h+r-t \|\|$	✗	✓	✓	✓	✗
RotatE	$-\|\|h \circ r-t \|\|^2$	✓	✓	✓	✓	✗
DistMult	$< h,r,t >$	✓	✗	✗	✗	✓

LITERATURE SURVEY

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- This Led us to our Base Paper “KG-Predict: A knowledge graph computational framework for drug repurposing”
- How well did KG-Predict outperformed the other state of art embedding methods ?

Data	Method	Hits@1	Hits@3	Hits@10	MRR
GP-KG	TransE	0.116	0.226	0.399	0.209
	DistMult	0.103	0.207	0.379	0.191
	ConvE	0.126	0.232	0.399	0.216
	RotatE	0.119	0.231	0.403	0.212
	KG-Predict	**0.174**	**0.266**	**0.447**	**0.261**

LITERATURE SURVEY

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- This Led us to our Base Paper “KG-Predict: A knowledge graph computational framework for drug repurposing”.
- The authors extended the Composition based multi regional graph Convolutional network (CompGCN).

LITERATURE SURVEY

- Let's take a look at the algorithm what the authors used
  - Input : Feature Vector x_v of node v (e.g. drug, disease) and feature vector S_r of edge r (e.g. Drug-treat-disease).
  - CompGCN Layer : The model Stacked several convolutional layers.
    - Used 2 different functions.
      - $AGGREGATE_n(.)$
      - $CONCAT(.)$
    - KG-Predict uses learnable transformational matrix W_{rel}^{n} which project all relations to same embedding space as entities and relations which are to update
  - Output : z_v represent the set of entity embedding and z_r represent the set of relation embedding

LITERATURE SURVEY

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Pseudo Code for the explained algorithm

Algorithm 1: GP-KG Embedding Algorithm

Input: $G = (V, E, X, R, S)$, $\forall n \in 1, 2, ..., N$, aggregator function $AGGREGATE_n(.)$, concat function $CONCAT(.)$, relation-specific coefficient matrix W^n_{rel}, self-specific coefficient matrix W^n_o, learnable transformation matrix W^n_{rel}, the set of entity v's neighbors $N(v)$.

Output: entity embedding Z_V, relation embedding Z_R.

$h^0_v \leftarrow X_v$, $h^0_r \leftarrow S_r$;

for $n = 1, 2, ..., N$ **do**

  for $v \in V$ **do**

    $h^n_{N(v)} \leftarrow AGGREGATE_n(W^n_\lambda \psi\left(h^{n-1}_u, h^{n-1}_r\right)), u, r \in N(v)$;

    $h^n_v \leftarrow f(CONCAT(h^n_{N(v)}, W^n_o h^{n-1}_v))$;

  for $r \in R$ **do**

    $h^n_r \leftarrow W^n_{rel} h^{n-1}_r$;

$Z_V \leftarrow \{h^N_v\}, \forall v \in V$;

$Z_R \leftarrow \{h^N_r\}, \forall r \in R$;

LITERATURE SURVEY

- How well did KG-Predict outperformed the other state of art embedding methods ?

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OBJECTIVE

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- Modify the GP-KG embedding process to construct a unique embedding methodology
- Investigate state-of-the-art embedding and make necessary alteration to them.
- Use Altered embedding to develop new technique and use them to find results on Prediction model.

THANKYOU