# COMPUTATIONAL DRUG REPOSITIONING USING KNOWLEDGE GRAPH AND AI


The LNM Institute of Information Technology

**Team Members**

| | |
|---|---|
| Om Gupta | 21ucs140 |
| Pitani Nitin Srichakri | 21ucs149 |
| Tarun Agarwal | 21ucs219 |

**Guided by**
**Dr. Abhijit Adhikari**

**Co-guided by**
**Dr. Poulami Dalapati**

# TABLE OF CONTENTS

# INTRODUCTION

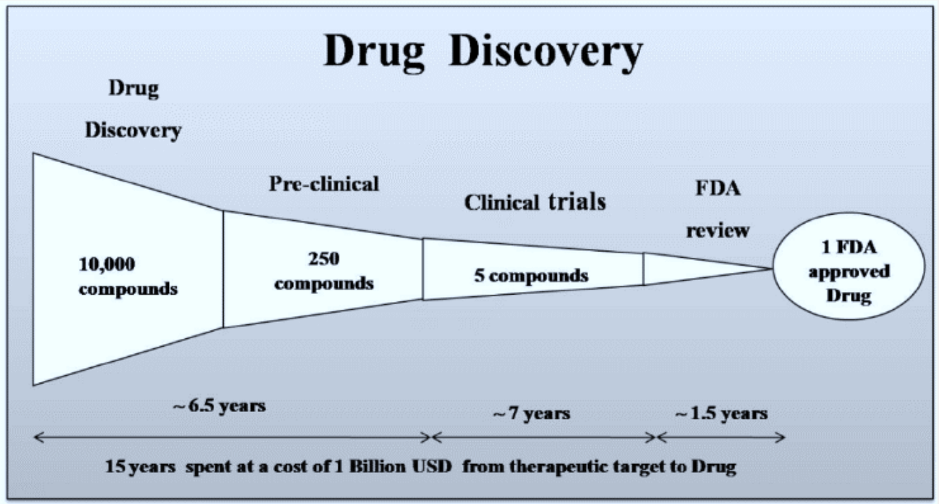
LNMIIT
The LNM Institute of Information Technology

- 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

LNMIIT
The LNM Institute of Information Technology

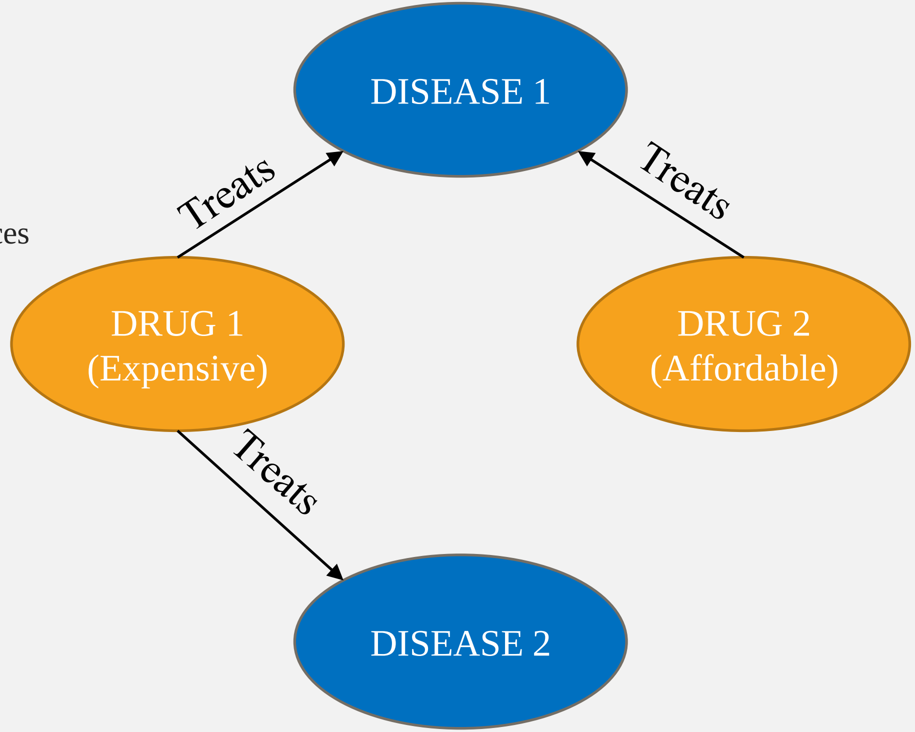
- Which tools can be used in perform the above task?
  - Clustering and Classification Algorithms
    - Meticulous analysis and pattern recognition by grouping similar compounds and predicting their efficacy efficiently identify potential drug candidates
    - Undergone extensive research and has reached 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

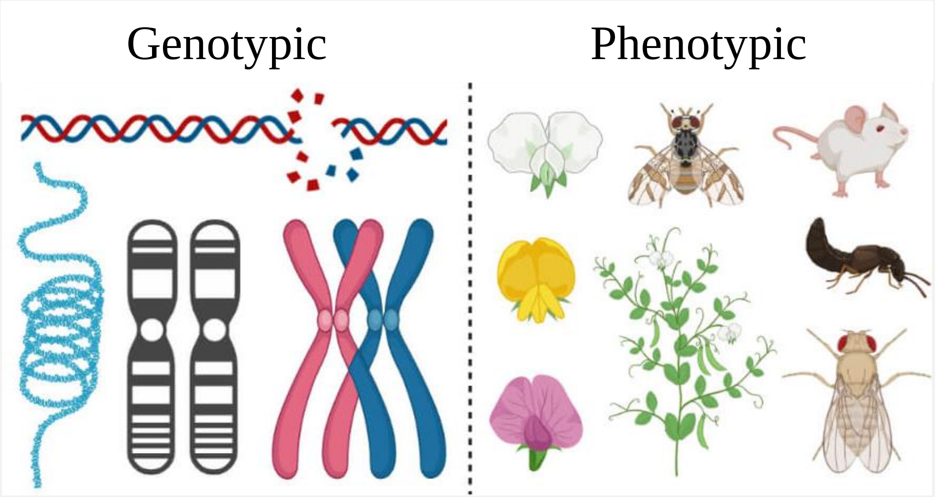
# SOME DEFINITIONS

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



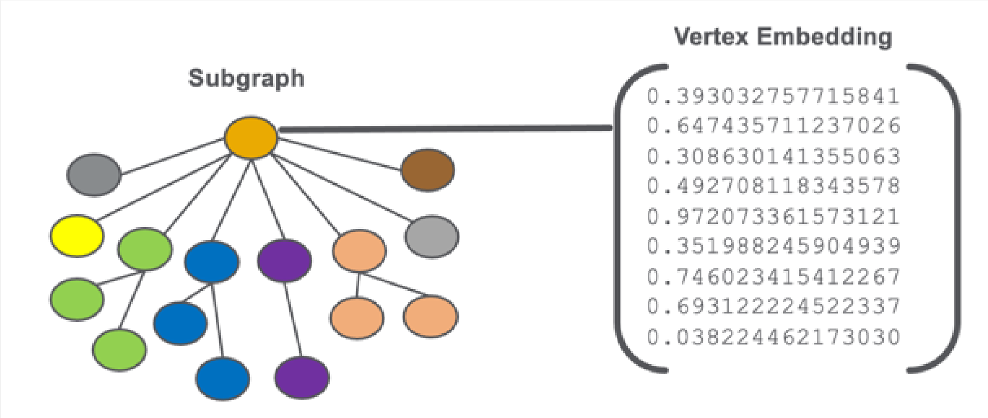
# SOME DEFINITIONS

- 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.



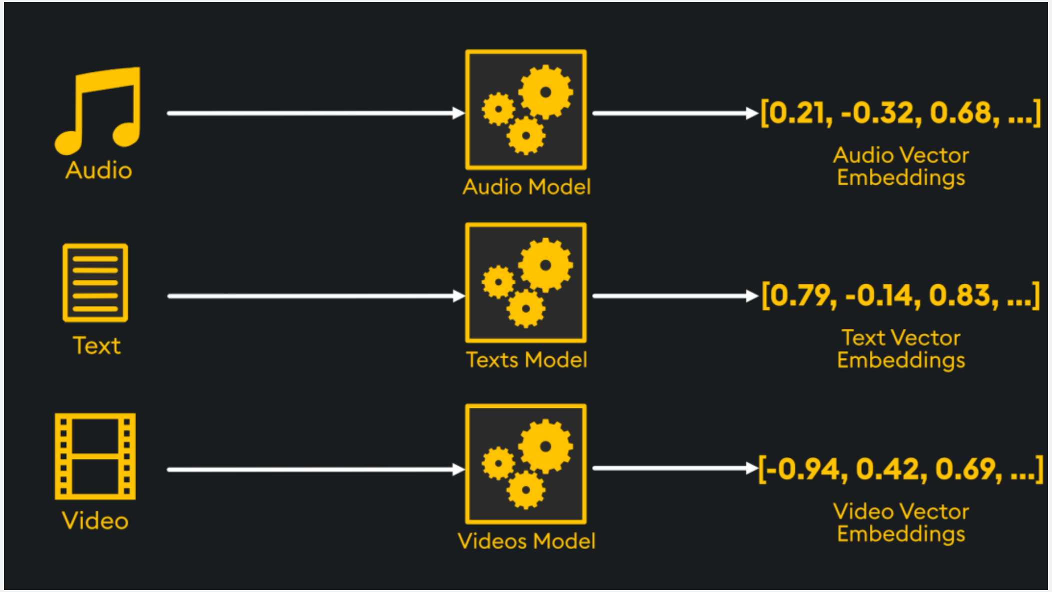
# SOME DEFINITIONS

- How do we use knowledge graph in algorithms?
- 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.



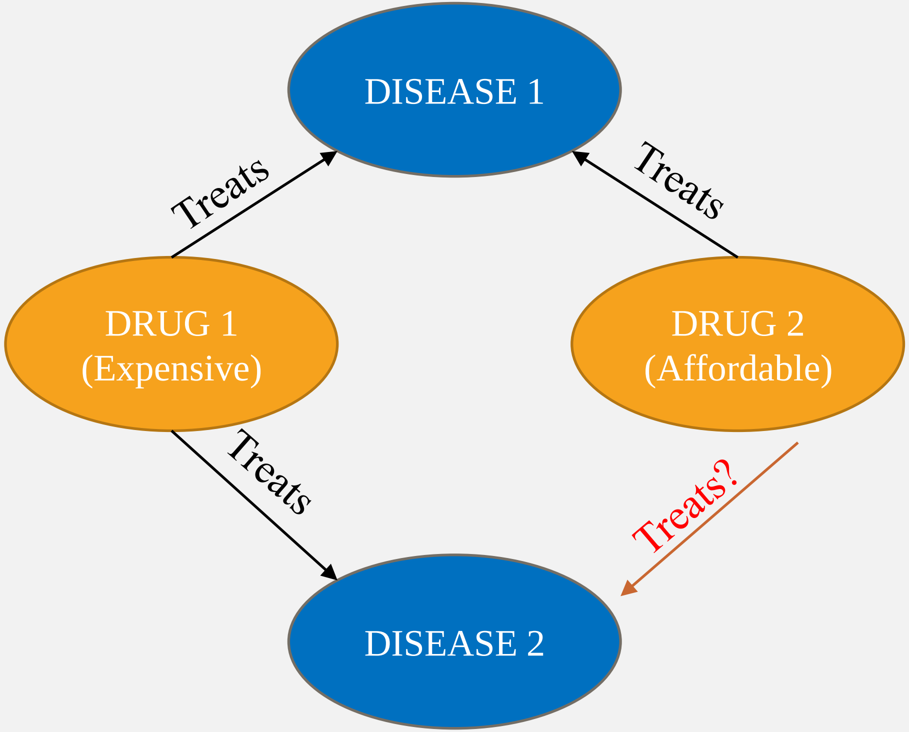
# SOME DEFINITIONS

- What do these Numbers Signify?



# SOME DEFINITIONS

- 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.



# SOME DEFINITIONS

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

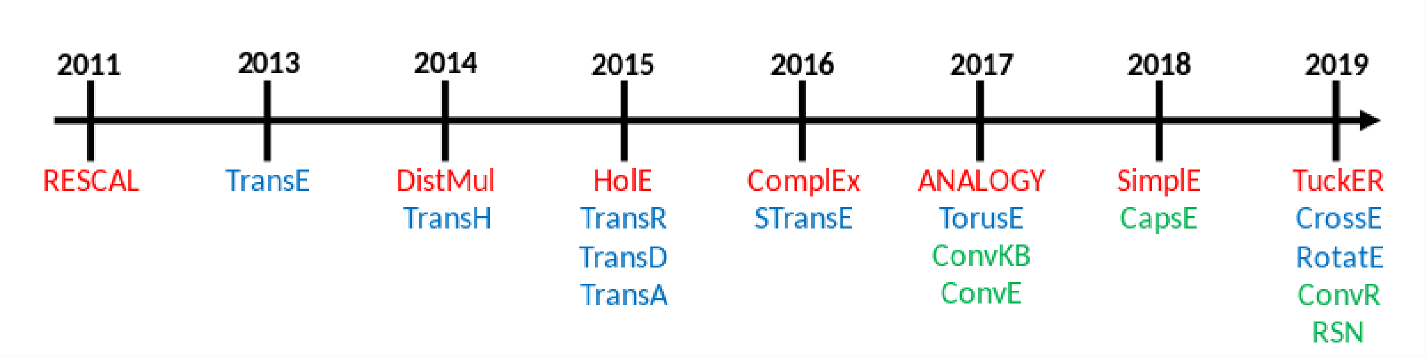
- Associate entities and relations with shallow embeddings
- Given a triple ($h$, $r$, $t$) the goal is that the embedding of ($h$, $r$) should be close to the embedding of $t$.
  - How to embed ($h$, $r$) ?
  - How to define score $f_r$ ($h$, $t$) ?
  - Score $f_r$ is high if ($h$, $r$, $t$) exists,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

# 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*

# LITERATURE SURVEY

- Timeline of different embedding models.



# LITERATURE SURVEY

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

# LITERATURE SURVEY

Four Relation Patterns (continued…):

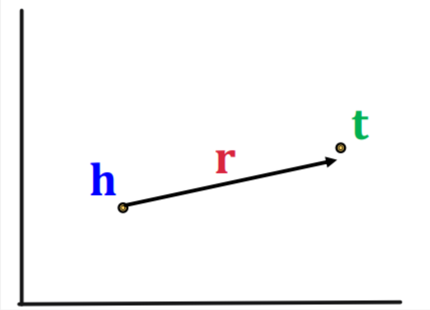
- Composition (Transitive) Relations:
  - $r_1(x, y)$ & $r_2(y, z) \Rightarrow r_3(x, z) \quad \forall x, y, z$
  - Example: My mother's husband is my father.

- 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*'

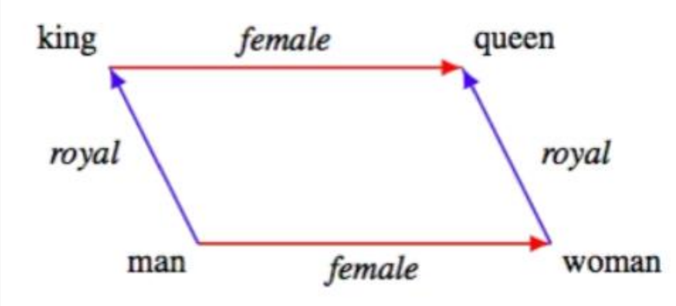
# LITERATURE SURVEY - TransE

The LNM Institute of Information Technology

- 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 $\boldsymbol{h} + \boldsymbol{r} \neq \boldsymbol{t}$

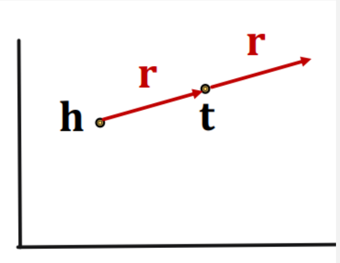



- Entity scoring function: $f_r(h, t) = -||\, h + r \;- t\, ||$



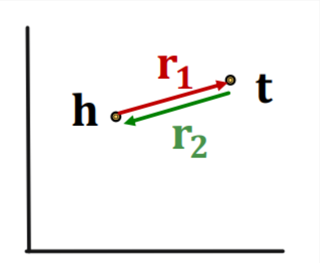
# LITERATURE SURVEY - TransE

LNMIIT
The LNM Institute of
Information Technology




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

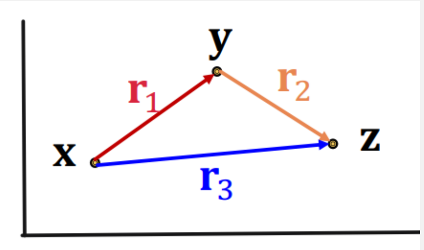
$h + r = t \; but \; t + r \neq h$




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

$h + r_2 = t$
*and we can set*

$r_1 = -r_2$

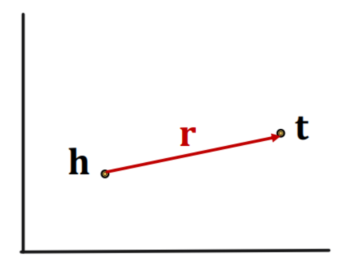


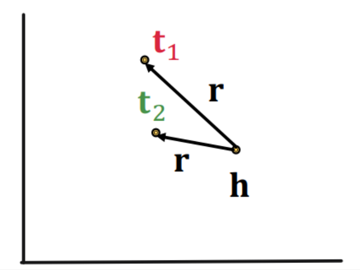

Composition:
$r_1(x,y) \,\&\, r_2(y,z)$
$\Rightarrow r_3(x,z) \quad \forall x,y,z$

$r_1 + r_2 = r_3$

# LITERATURE SURVEY - TransE

Limitations :




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.

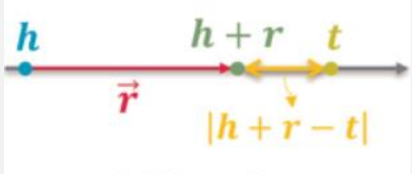
$t_1 = h + r = \; t_2$

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

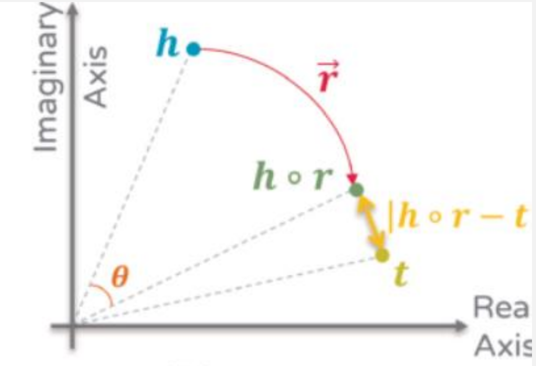
# LITERATURE SURVEY -RotatE

- 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 - $\boldsymbol{h} \circ \boldsymbol{r} \approx \boldsymbol{t}$
    - else $\boldsymbol{h} \circ \boldsymbol{r} \neq \boldsymbol{t}$
    - where '∘' is the Hadamard product on the embeddings.

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



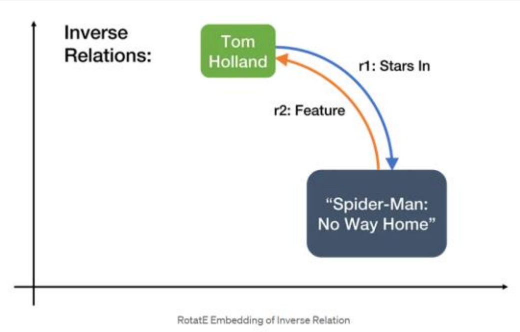
(a) TransE

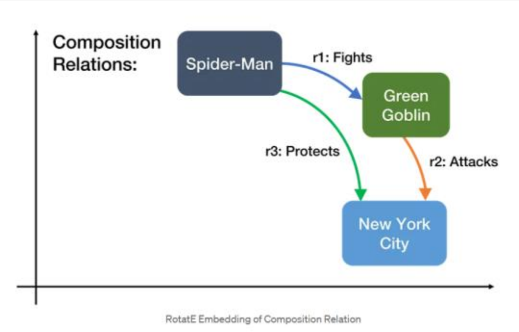


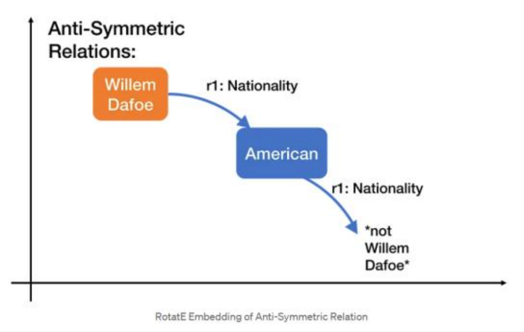
(b) RotatE

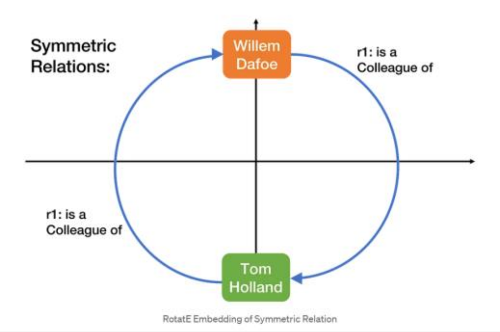
The Hadamard product is a binary operation that takes in two matrices of the same dimensions and returns a matrix of the multiplied corresponding elements.

# LITERATURE SURVEY -RotatE



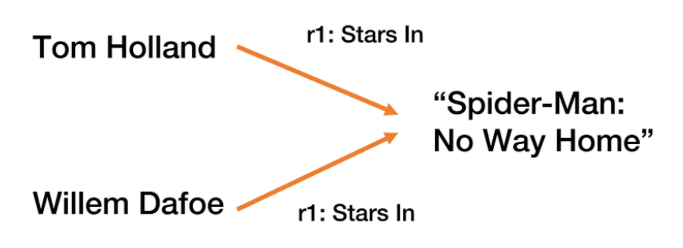



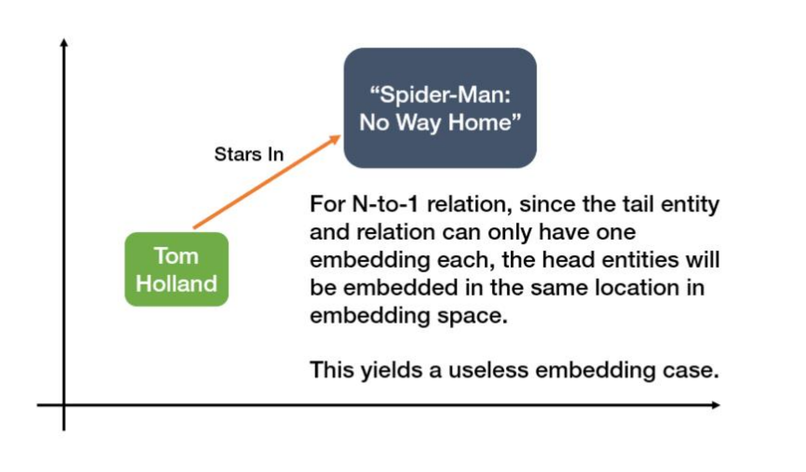

RotatE can model symmetric relations that TransE cannot express! It does so as 180-degree rotations.

# LITERATURE SURVEY -RotatE

Limitations :




Knowledge Graph with N-to1 Relation



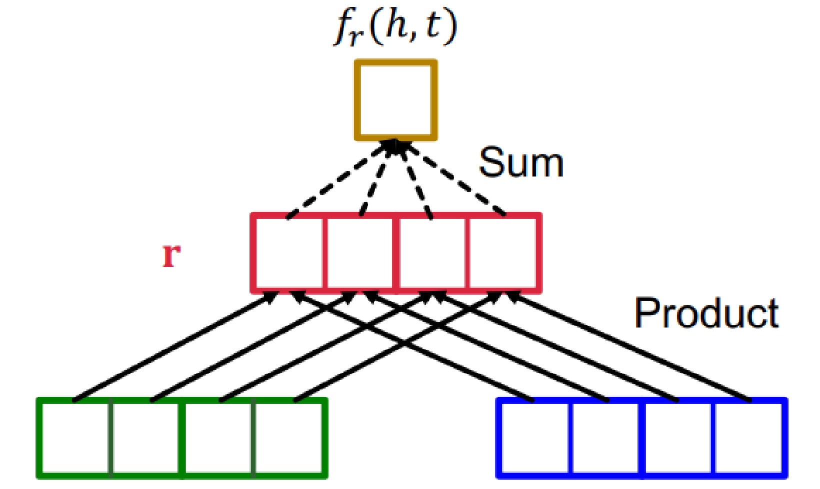

TransE Embedding of N-to-1 Relation

# LITERATURE SURVEY -DistMult

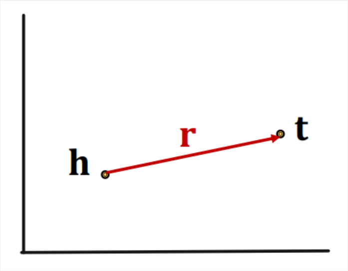
- For a triple ($h$, $r$, $t$), let $\boldsymbol{h}, \boldsymbol{r}, \boldsymbol{t} \in \mathbf{R}^{\mathbf{d}}$ be embedding vectors.

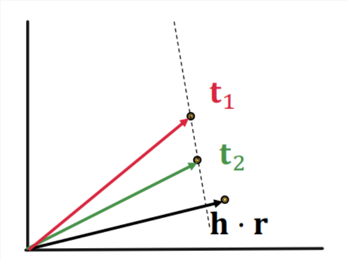
- Score function: $f_r(h,t) = < h, r, t >$
  $= \sum_i \; h_i \,.\, r_i \,.\, t_i$

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



# LITERATURE SURVEY -DistMult




Symmetric:

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

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

1-to-N:

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

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

# LITERATURE SURVEY -DistMult

LNMIIT
The LNM Institute of
Information Technology

## 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

# LITERATURE SURVEY

LNMIIT
The LNM Institute of Information Technology

Summary of different embedding techniques:

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

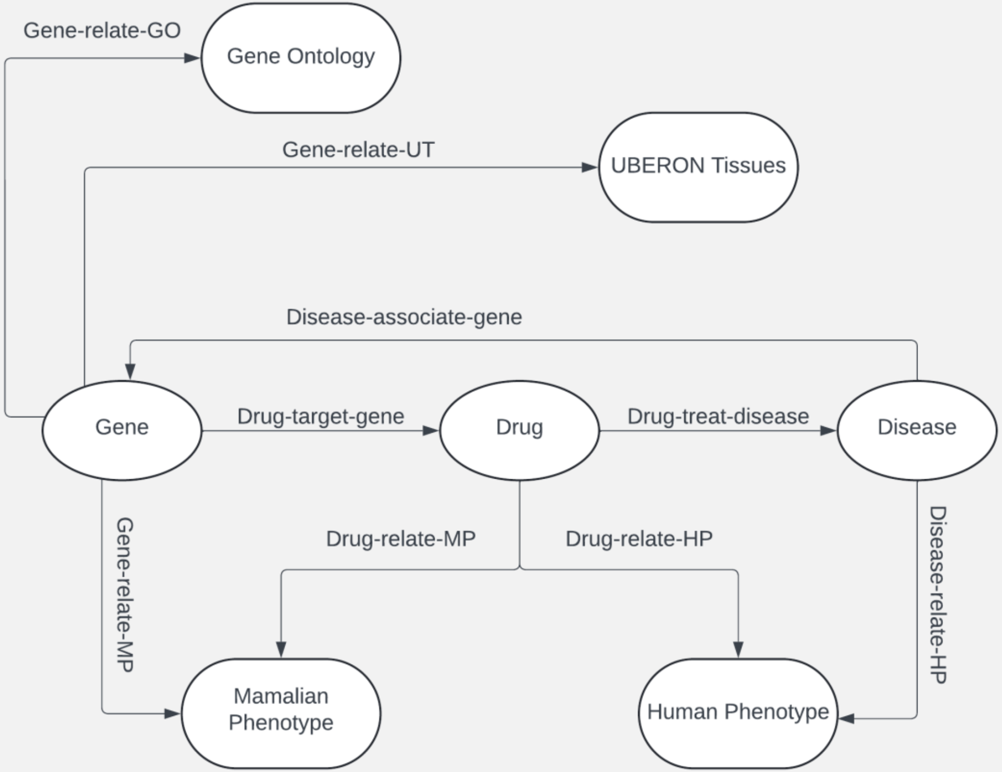
# LITERATURE SURVEY

- 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

- 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



# LITERATURE SURVEY



- Let's take a look at the embedding algorithm 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

The LNM Institute of Information Technology

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 ?

| 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** |

# OBJECTIVE

- 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