Predicting Potential Drug Targets Using Tensor Factorisation and Knowledge Graph Embeddings

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ABSTRACT
The drug discovery and development process is a long and expensive one, costing over 1 billion USD on average per drug and taking 10-15 years. To reduce the high levels of attrition throughout the process, there has been a growing interest in applying machine learning methodologies to various stages of drug discovery process in the recent decade, including at the earliest stage – identification of druggable disease genes. In this paper, we have developed a new tensor factorisation model to predict potential drug targets (i.e., genes or proteins) for diseases. We created a three-dimensional tensor which consists of 1,048 gene targets, 860 diseases and 230,011 evidence attributes and clinical outcomes connecting them, using data extracted from the Open Targets and PharmaProjects databases. We enriched the data with gene representations learned from a drug discovery-oriented knowledge graph and applied our proposed method to predict the clinical outcomes for unseen gene target and disease pairs. We designed three evaluation strategies to measure the prediction performance and benchmarked several commonly used machine learning classifiers together with matrix and tensor factorisation methods. The result shows that incorporating knowledge graph embeddings significantly improves the prediction accuracy and that training tensor factorisation alongside a dense neural network outperforms other methods. In summary, our framework combines two actively studied machine learning approaches to disease target identification, namely tensor factorisation and knowledge graph representation learning, which could be a promising avenue for further exploration in data-driven drug discovery.

CCS CONCEPTS
• Computing methodologies → Factorization methods; Knowledge representation and reasoning.

KEYWORDS
drug discovery, tensor factorisation, knowledge graph

1 INTRODUCTION
The discovery and development of drugs is a complex process that aims to identify pharmalogical agents that are therapeutically effective for curing or treating diseases. According to the US Food and Drug Administration (FDA), on average, it takes approximately 12 years to get a newly discovered drug into the market and the cost is 1.3 billion USD [1]. There are many factors that contribute to the high cost of developing a drug: significant time and resources invested in target identification and the validation process, multiple early tests for a considerable number of promising compounds and complex in vitro and in vivo studies to understand the drug toxicity, to just name a few. Among all these factors, clinical research is arguably the most critical and costly process. According to AstraZeneca, between the year 2005 and 2010, the success rate of preclinical projects in the company was 66% while for Phase I, II, and III clinical projects, the rates dropped to 59%, 15% and 60%, respectively [9]. To raise the success rates of clinical projects and consequently, reduce the time and cost needed for developing a drug, it is imperative to develop an effective method to predict whether a candidate drug target is clinically promising for treating a disease on a large scale.

Traditionally, scientists identify new drug targets by discovering novel insights into a disease mechanism from research publications and lab experiments, which in turn allows scientists to design a drug molecule to activate or inhibit the gene target in order to cease or reverse the disease effects [15] and by repositioning existing drugs to find unanticipated but beneficial effects against other diseases [27]. Together, these processes have generated a large number of therapeutic hypotheses which are further supported by an enormous amount of both structured and unstructured evidence data. It is then of great interest to explore how we can better exploit such a wealth of information to identify and prioritise drug targets for diseases in an accurate and computationally efficient manner, using state-of-the-art data science technologies.
Machine learning is a natural candidate for the challenge. The gene target-disease pairs can be viewed as data points and their clinical trial outcomes as binary labels – success or failure. The biological evidence, from research publications, lab experiments, etc., that associates gene targets with diseases are used as features. However, there are several major difficulties in framing this as a standard binary classification problem. First, there are very few true positives – in Open Targets and PharmaProjects databases, less than 0.01% gene target-disease pairs have approved drugs [3, 21]. Second, the feature space (biological evidence attributes) for pairs of gene targets and diseases is extremely sparse. In the September, 2020 version of Open Targets, there are in total 6,551,303 associations, which are extracted from 20 data sources, connecting 27,610 gene targets and 13,944 diseases. In other words, as high as 98.3% of the gene target-disease pairs have no biological evidence at all. As a consequence, the traditional feature-in, prediction-out machine learning models might be incompetent in this context.

In this paper, motivated by the recent work [36], we explore whether tensor factorisation can be used as a powerful tool for addressing the aforementioned challenges. Mathematically, a tensor is a higher order generalisation of a vector (first order tensor) and a matrix (second order tensor) in which each dimension corresponds to an axis or a mode. A 3-mode tensor is therefore a natural representation to host the biological data in our analysis where the modes correspond to gene targets, diseases and their association evidence, respectively. The clinical outcomes are represented as an additional slice along the evidence mode. To predict the missing values in the clinical outcome slice, we have developed a novel tensor factorisation method that utilises gene target representations learned from a drug discovery-oriented knowledge graph as side information. To the best of our knowledge, this is the first tensor factorisation framework that incorporates biomedical knowledge graphs for the purpose of predicting potential drug targets for diseases. To aid in reproducibility, we release all the processed public data sets and model training scripts ¹.

The remainder of the paper is organised as follows. In Section 2, we review recent tensor factorisation applications in drug discovery and development. In Section 3, we first describe our data collection and processing procedures and introduce how we use knowledge graphs and gene target embeddings in the developed framework. We then explain in detail our proposed tensor factorisation model and describe the benchmarking strategies and experimental setup in Section 4. In Section 5 we present the results of our experimental evaluation. Finally, in Section 6 we present our conclusions, discuss the contribution and limitations of our work, and highlight several future research directions.

2 LITERATURE REVIEW

In recent decades, tensor factorisation has found many useful applications in a wide range of machine learning areas, such as recommender systems, image processing and computer vision, and natural language processing [4, 12, 23, 31, 39]. Such success has led to a growth in the use of tensor factorisation for addressing biomedical challenges in recent years. For instance, Chen and Li [6] proposed a tensor decomposition model to predict the therapeutic benefits of drug combinations. In particular, a 3-mode tensor was constructed to represent comprehensive relationships between drugs and diseases as well as their similarity information. The molecular mechanisms of drug synergy can thus be well revealed via simultaneously factorising the coupled tensor and similarity matrices. The authors later applied the technique to model relational drug-gene target-disease interactions and successfully showed that the model outperforms some competitive methods at predicting drug mechanism of actions [7]. To address the data sparsity and scalability challenges, Macau, a powerful, flexible and scalable Bayesian multi-relational factorisation method for heterogeneous data has been developed [29]. One unique advantage of Macau is that it enables the incorporation of side information, specifically entity and relation features, which is essential for complex tasks such as drug-protein activity prediction. More recently, Yao et al. [36] have applied Macau to the problem of predicting clinical outcomes of therapeutic hypotheses and have also tested the performance of several other machine learning models including Logistic Regression, LASSO, Random Forest, Matrix Factorisation and Gradient Boosting Machine. The result suggested that tensor factorisation is comparable or better than the baseline methods in various cross-validation scenarios.

The importance of gene target side information in matrix and tensor factorisation has been discussed by Piro and Di Cunto [25]. In the paper, they have examined a number of disease gene prioritisation tools that utilise different types of evidence including text-mining of biomedical literature, functional annotations, pathways and ontologies, phenotype relationships, intrinsic gene properties, sequence data, protein–protein interactions, regulatory information, orthologous relationships and gene expression information. Generally speaking, most existing methods incorporate gene target side information by either directly merging data from different sources or applying techniques such as principal component analysis (PCA) to evidence data [20, 32]. However, such ways of using side information do not fully exploit the interconnections between genes and other biological entities and dimensionality reduction technologies such as PCA cannot capture the essential gene representations in the high-dimensional, heterogeneous data. To address this challenge, we utilise a biomedical knowledge graph, Hetionet [14], which is an integrative network of biomedical knowledge centered around genes and diseases assembled from different databases, and use gene representations automatically learned from the graph (known as knowledge graph embeddings [33, 34]) as the gene target side information in our proposed model. We show that by connecting different biological resources via a well-structured knowledge graph and by learning gene representations which contain essential information not only from gene–gene interactions and gene–disease associations but the biomedical knowledge field, the prediction performance can be improved.

3 METHOD

3.1 Data Collection and Processing

We have created a dataset which combines clinical outcomes from the commercial database CiteLine PharmaProjects [3] and evidence from the open-source database Open Targets [21] between gene

¹Code will be available: https://github.com/AstraZeneca/
targets and diseases (this is detailed in Table 1). PharmaProjects has curated lists of clinical trials specifying the drug being tested, the targeted proteins and the disease being tested against. We joined these two datasets together to create a mapping of diseases to gene targets. We defined that the clinical outcome of a gene target and a disease is positive if there has been at least one successful clinical trial for the pair in the PharmaProjects database. On the other hand, the clinical outcome is negative if there is no clinical success and at least one failed clinical trial. Open Targets has seven different data types, each with an association score, for each gene target-disease pair. We therefore used Open Targets to create the evidence data between targets and diseases.

One major challenge occurring when combining the two data sets was that PharmaProjects uses the MeSH Ontology [17] for diseases while Open Targets uses the Mondo Ontology [19]. To address this problem, we used the EMBL-EBI Ontology matching tool OXO [2] to connect these MeSH and Mondo terms.

We finally obtained a three-dimensional tensor in which the first two dimensions correspond to 1,048 gene targets and 860 diseases, respectively and the third dimension presents their evidence and clinical outcomes (230,011 in total), which is depicted in Figure 1. The tensor is binary, i.e., all of its entries are either 0 or 1, indicating whether or not a gene target-disease pair is linked by some evidence type or by the outcome of clinical trials. The tensor is extremely sparse, with density equal to just 3.19%.

![Figure 1: A tensor representation of the biological dataset](image)

3.2 Knowledge Graph and Gene Target Embeddings

Generally speaking, a knowledge graph is an integrative network representation of structured and unstructured knowledge, which provides an easier way of capturing complex semantic relationships than conventional databases. For instance, in a biomedical knowledge graph, various biological entities are modelled as nodes, whilst millions of complex biomedical relationships are modelled as edges (links) connecting nodes [5]. In recent years, many researchers and pharmaceutical companies have been building biomedical knowledge graphs to address various drug discovery challenges, e.g., Hetionet [14], PharmKG [38] and Rosalind’s knowledge graph [22].

In this paper, we make use of Hetionet, which is one of the earliest integrative biological networks centred around genes and diseases and now forms the core of many more recently developed disease knowledge graphs, and learn effective feature representations of gene targets using various knowledge graph embedding techniques. Hetionet contains 47,031 biological entities of 11 types (Gene, Disease, Compound, Pathway, Anatomy etc.) and 2,250,197 relationships of 24 types (Disease-associates-Gene, Compound-treats-Disease, Gene-participates-Pathway, etc.) integrated from 29 public databases. The graph models the complex interactions between genes and other genes, diseases, compounds, pathways, biological processes and many other entities, so the learned embeddings are able to capture interactive characteristics of genes in the biomedical field (see Figure 2). We therefore used the gene embeddings to enrich the gene target information in our data set and treated them as side information in the tensor factorisation framework to help improve the prediction accuracy.

3.3 Tensor Factorisation with Knowledge Graph Embeddings

To predict the missing values in the clinical outcome matrix in the data tensor, we adopted a tensor factorisation model which factorises the data tensor into a core evidence tensor and two latent gene target and disease matrices which need to be learned, as depicted in Figure 3. These together with the gene target representation matrix learned from the knowledge graph were then fed into a dense neural network to generate the output, which will be the predicted value for the clinical outcome of a gene target-disease pair.

We denote $D = \{D_1, ..., D_n\}$ the set of diseases and $T = \{T_1, ..., T_n\}$ the set of gene targets present in the data set and the association score of evidence type $k$ between disease $D_i$ and gene target $T_j$ is represented as $E_{ijk} \in [0,1]$. Similarly, the clinical outcome between disease $D_i$ and gene target $T_j$ is denoted as $X_{ij} \in [0,1]$. Let the learned latent variables for diseases and gene targets, and the gene target knowledge graph embeddings be $U, V, W$, respectively. Then the probability of a successful clinical outcome between disease $D_i$ and gene target $T_j$ is calculated as follows:

$$P(X_{ij} = 1 | \text{e}_{ij}, u_i, v_j, w_j) = f(\text{concat}(\text{e}_{ij}, u_i, v_j, w_j)),$$

(1)

where $\text{e}_{ij}, u_i, v_j, w_j$ are the evidence vector between $D_i$ and $T_j$, latent variables for $D_i$, latent variables for $T_j$, and gene target representations learned from the knowledge graph for $T_j$, respectively. These vectors are concatenated together before being input into the function. We define the function $f$ to be a feed-forward neural network with 2 dense hidden layers of 256 and 64 neurons, both using the ReLU (Rectified Linear Unit) activation function. The output layer uses a linear activation function.

The dimensionality of the gene target and disease parameter matrices is $V \in \mathbb{R}^{T \times d}$ and $U \in \mathbb{R}^{D \times d}$, where $d$ is the size of the embedding for each entity - set to 32 for this work. We have also explored other dimensionality numbers but found no significant difference in the result. Meaning that together, these matrices contribute 61,056 learnable parameters to the model. The neural network, if using a 32-dimensional Hetionet embeddings has 43,240 parameters. This results in final total model size of just over 100,000...
Table 1: Gene Target-disease evidence types in Open Targets.

| Evidence Type          | Association Score Sources                                      | Description                                                                                                                                 |
|------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Genetic Associations   | ClinVar (EVA), PheWAS Catalog, Gene2Phenotype, Genomics England PanelApp, Open Targets Genetics Portal, UniProt literature, ClinGen | Curated and calculated associations between genetic variants and mendelian-inherited diseases, common diseases and phenotypes/traits.             |
| Somatic Mutations      | Cancer Gene Census, ClinVar somatic (EVA), IntOGen            | Somatic mutations noted in cancers and other diseases.                                                                                      |
| Drugs                  | ChEMBL                                                          | Database of known drugs and other pharmacological agents linked to bioactivity assay data and disease (where applicable).                      |
| Pathways and Systems Biology | Reactome, Sysbio, SLAPenrich, PROGENy, Project Score (CRISPR) | Gene sets comprised from curated biological pathways, and oncology-centric resources (CRISPR gene function screens and pathway activities inferred from gene expression data). |
| RNA Expression         | Expression Atlas                                              | Gene expression data from different biological conditions (e.g. normal and disease).                                                       |
| Text Mining            | EuropePMC                                                      | Co-occurrences between gene target and disease terms, text mined from PubMed and PubMedCentral.                                             |
| Animal models          | PhenoDigm                                                      | Associations between gene targets and diseases, inferred from similarities between human disease characteristics and phenotypes observed in mouse models where the gene is perturbed. |

Figure 2: Schema of knowledge graph embeddings.

Learnable parameters. These parameters were optimised using the Adagrad [35] variant of Stochastic Gradient Descent (SGD) with Mean Squared Error (MSE) as the loss function. The model was trained for 100 epochs, using a batch size of 2,000 and a learning rate of 0.05.

We argue that the main advantage of this proposed technique is that the dense neural network allows for complex interactions between the Open Targets evidence, the latent variables and the pre-trained knowledge graph embeddings. In this way the embeddings from the knowledge graph can have non-linear interactions with the prediction outcome and can interact with both the disease and the gene target latent variables. This would not be happening if the embeddings were used as side information in algorithms such as Macau [29].
We used the following techniques to generate the embedding matrix $W$ for gene targets from the Hetionet knowledge graph. All the algorithms were set to use embedding dimension of 32 and were trained using the default parameters reported in the respective paper. Node2vec, a homogeneous graph embedding method that groups nodes with similar neighbourhoods together [11]; Metapath2vec, a heterogeneous graph embedding method that groups nodes of the same type with similar neighbourhoods together [10]; Graph Variational Auto-Encoder (GVAE), a homogeneous graph-based embedding approach that tries to predict links between nodes by applying a convolutional operation to latent variables of node neighbours [16]; ComplEx, a heterogeneous graph-based embedding approach that tries to predict links between nodes by applying a decoder operation between latent variables of node pairs [30]; Random embeddings, which are randomised vectors that can be compared with others to measure the random effects on the prediction performance.

4 EXPERIMENTAL SETUP

4.1 Datasets Overview

The three-dimensional tensor used in the experiments, which was constructed from the Open Targets and PharmaProjects databases, contains 1,048 gene targets, 860 diseases and 230,011 evidence attributes and clinical outcomes connecting them. The drug discovery-oriented knowledge graph Hetionet, which is used to enrich the side information of gene targets, consists of 47,031 biological entities and 2,250,197 relationships integrated from 29 public databases.

4.2 Evaluation Strategies

We used three cross-validation strategies to assess the accuracy of predicting the unseen clinical outcomes of gene target and disease pairs. The first randomly split all the gene target-disease pairs into five folds. We trained the models on four folds and tested on the remaining fold. This is the standard cross-validation procedure; however, it could result in the case that gene target-disease pairs that share the same gene target, or the same disease are assigned to different folds, and thus introduce bias when measuring the performance. This is because if one gene target has been clinically successful for a particular disease, then it is likely to be successful for another closely related disease. Similarly, if a disease is treated well by a particular gene target then it is likely to be treated well by another similar gene target.

To overcome this issue, we designed a second strategy where we first randomly assign gene targets into one of five groups. Gene target-disease pairs are then put into the fold the gene target is assigned to. We then again trained the models on four groups and tested on the remaining group. Lastly and similarly, we split all diseases into several classes depending on which part of the human body the disease affects. The gene target-disease pairs are then put into the class the disease is assigned to.
4.3 Baseline Models

We applied the following classic machine learning classifiers to the data. Logistic regression, a simple linear model using the Scikit-Learn implementation [24]; k-nearest neighbours classifier using the Scikit-Learn implementation [24]; Random forest, an ensemble method using the Scikit-Learn implementation [24]; Gradient boosting machine using the XGBoost implementation [8]. We also applied Macau Bayesian Probabilistic Matrix Factorisation (BPMF) to the reduced matrix which contains only gene targets, diseases and their clinical outcomes, and used Macau tensor factorisation [29] as well.

4.4 Performance Metrics

Two metrics have been used to assess the prediction performance of the evaluated methods: Area Under Receiver Operator Curve (AUROC) and Area Under Precision-Recall Curve (AUPRC). The former is normally used to measure how well a classifier can distinguish between a positive sample and a randomly selected negative sample in a binary classification problem while the latter assesses the probability that if a positive sample is selected from the ranked list produced by a method, all samples ranked above it are positive.

5 RESULTS

5.1 Evaluating Baseline Models

In this experiment, we evaluated the prediction performance of our proposed tensor factorisation method by comparing with the baseline models. In particular, we used the following set of features for each of the baseline classifiers including:

- **Control**: here only random numbers are used as gene target-disease evidence.
- **No Embedding**: here no embeddings are used and only the Open Targets gene target-disease evidence is present.
- **With Embedding**: a combination of Open Targets gene target-disease evidence and various gene target graph embeddings.

We used all of the three cross-validation strategies and the result (with mean and standard deviation) is reported in Figure 4. The most striking trend in the figure is that in all three evaluation scenarios, our method outperforms all the baseline models by a significant margin (over 0.2 in AUROC and over 0.3 in AUPRC, on average), demonstrating the superiority of the tensor factorisation method. Several other important observations can be made. First, as we suspected, it is indeed much easier to make predictions using the random split benchmark than the disease or gene target split benchmark. This is because in the random split, the algorithms are more likely to have trained on similar pairs of gene targets and diseases, which tend to have a higher success rate if one of them is a success. We believe that the disease split and gene target split scenarios may give a more realistic indication of success chance and are thus more relevant. Second, in the disease and random split cases, there is a significant improvement in performance by including some type of gene target-level embeddings. This could be because the embeddings uniquely identify the gene targets and therefore allow the classifiers to “memorise” the successful drug targets for a particular disease and make accurate prediction for other similar gene targets for that disease.

Comparing the performance of the various graph embedding approaches more closely, some interesting observations can be made. For example, on the disease and random splits, it can be seen that the choice of the graph embedding has little impact on the over predictive performance – apart from the RGCN embeddings, which results in significantly worse performance overall. On the gene target split, both the Metapath2vec and Node2vec embeddings outperform the others.

5.2 Evaluating Matrix and Tensor Factorisation Methods

In this experiment, we compared our proposed tensor factorisation method with Macau Bayesian probabilistic matrix factorisation and Macau tensor factorisation [29]. The gene target representations in our method are the Metapath2vec embeddings. We again used all three evaluation strategies, and the results are highlighted in Figure 5. The figure demonstrates that in the disease and gene target split scenarios, our model clearly outperforms both the Bayesian matrix and tensor factorisation methods, which shows how incorporating knowledge graph embeddings into the tensor factorisation can lead to better overall predictive performance. However, our approach is just on par with the Macau tensor factorisation on the random data split, slightly outperformed by the matrix factorisation method.

5.3 Training Times

All models were trained on an Intel(R) Xeon(R) Gold 6252 CPU @ 2.10GHz with 32 cores. The training time (see Table 2) of our model is approximately 50% faster than Macau tensor factorisation, but it is slower than both the baselines and Macau matrix factorisation. However, we argue that the predictive performance gain of our model outweighs the computational burden.

5.4 Evaluating top gene target-disease predictions

In order to gain some subjective insight into our model predictions, we examined the top 7 gene target-disease predictions (ranked by prediction score) that were not present in the PharmaProjects data set, and that were present in all 3 data splits (random, disease and protein) (see Table 3). Interestingly, we see a mixture of disease types, and different subtypes of some of the diseases (e.g. primary and secondary hypertension). This suggests that the predictions aren’t simply dominated by prominent information types expected in biomedical literature (e.g. many different subtypes of solid tumour). On closer examination, some of the predicted relationships...
would appear to have some initial plausibility, for example the gene CASR is involved in calcium homeostasis [13, 26], an important aspect of bone biology, and SCN5A is noted to be involved in cardiac function with a noted link to heart disease [28, 37]. Of course this initial superficial assessment of the predictions highlights the challenge of interpretability of such approaches, in which improvements will help us better understand the value and risks in such predictions. Further work is planned in this area.
interesting line of investigation would be to design a more rigorous benchmarking strategy such as using well-curated disease databases for a handful of diseases of interest. Finally, the prediction improvements shown by utilising graph embeddings suggests there is still much to explore at the intersection between data modelling and graph composition, and algorithm application.

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### Table 3: Common predicted gene target-disease pairs in all three evaluation methods

| Rank | Gene Target-Disease Pair |
|------|--------------------------|
| 1    | CASR - osteoporosis      |
| 2    | CASR - congestive heart failure |
| 3    | SCN5A - secondary hypertension |
| 4    | SCN5A - primary hypertension |
| 5    | IFNAR2 - macular degeneration |
| 6    | CHRM2 - lymphocytic colitis |
| 7    | ADCY9 - irritable bowel syndrome |

6 DISCUSSION AND CONCLUSION

To help facilitate the identification of potential drug targets at the early stage of drug discovery and development, in this paper we processed gene target-disease evidence data from the Open Targets platform as well as clinical trial data from PharmaProjects database and employed standard machine learning classification algorithms and both matrix and tensor factorisation techniques to predict the clinical outcomes of unseen gene target-disease pairs. We adopted a new scheme when training the tensor factorisation method, i.e., alongside with a deep neural network, and showed that this outperforms many baseline models. Another main finding is that by using gene target representations learned by biomedical knowledge graph embedding algorithms as side information, the tensor factorisation performance can be dramatically improved, compared with traditional approaches where the side information only contains limited gene expression or protein-protein interaction data.

There are a number of limitations of the work reported. First, we did not distinguish between various types of negative samples (i.e., failed gene target-disease clinical trials) in the collected data. In reality, the data negativeness is highly variable – multiple reasons could be responsible for the failure of a clinical trial: drug safety (toxicology or clinical safety), drug efficacy (failure to achieve sufficient efficacy), pharmacokinetics/pharmacodynamics (PK/PD), commercial benefits, company strategy, etc [18]. These complex scientific and non-scientific factors make it difficult to obtain the true negative samples. In the future it would therefore be helpful to take this into consideration and classify the negative samples in the training set. Second, we treated all the positive samples, i.e., successful clinical trials, equally important in the training, however in practice, there exists some data that is more trustworthy than others. Hence, it would be important to take this into account when training the model by assigning different weights to different positive data points and penalise more if the model predicts the highly weighted data incorrectly. Third, in our framework we only used side information for gene targets, it would be helpful in the future to exploit disease and evidence side information such as disease similarities, via embeddings learned from knowledge graphs.

Our work could be extended in several ways. For instance, it would be interesting to take into consideration more biological data sets such as ChEMBL to further enrich the gene target-disease-evidence tensor, which will help reduce the data sparsity. Another
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