

## Specific Tuning Parameter for Directed Random Walk Algorithm Cancer Classification

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**Abstract**— Accuracy of cancerous gene classification is a central challenge in clinical cancer research. Microarray-based gene biomarkers have proved the performance and its ability over traditional clinical parameters. However, gene biomarkers of an individual are less robustness due to litter reproducibility between different cohorts of patients. Several methods incorporating pathway information such as directed random walk have been proposed to infer the pathway activity. This paper discusses the implementation of group specific tuning parameter in directed random walk algorithm. In this experiment, gene expression data and pathway data are used as input data. Throughout this experiment, more significant pathway activities can be identified which increases the accuracy of cancer classification. The lung cancer gene is used as the experimental dataset, with which, the sDRW is used in determining significant pathways. More risk-active pathways are identified throughout this experiment.

**Keywords**— directed random walk algorithm; group specific tuning parameter; cancer classification

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### I. INTRODUCTION

The human genome contains tens of thousands of genes. Throughout studying the genes, biologists and researchers can understand more about human beings, especially the causes of formation of cancer [1]. The study and analysis of these genes are done by using microarray experiment. Genes are playing important roles in the classification of cancer and for prognosis or diagnosis of cancer at early stage. The analysis and study of genes are complete by using deoxyribonucleic acid (DNA) microarray analysis. DNA microarray analysis is a technology used by scientists to measure the gene expression level changes in gene expression data. The microarray analysis involves the breaking of a cell to isolate its genetic contents to identify all the genes that are turned on in that cell, and generating a list of those genes (DNA Microarray). Various experiments and approaches are triggered to identify informative genes and pathways that contribute to the certain cellular process [2]. Even though the gene expression data contain genetic information, it is not sufficient to classify cancer accurately due to the small sample size of data. Hence, the integration between pathway data and gene expression data can provide a better understanding of the biological processes for cancer classification [3]. Biologists and researchers need accurate classification tools and lists of cancerous genes, which can contribute to the diagnosis process.

The Directed Random Walk (DRW) was proposed by Liu in 2013. It was developed to infer reproducible pathway activities and robust disease classification [4]. Its' computational complexity and existing algorithm identify genes within pathways, which led to over-fitting and poor discriminating power. The discriminating power reflects the reproducible power and the robustness of pathways, whether the pathways are significantly differentially expressed or not [4]. Global directed pathway network is constructed in a directed random walk. In directed random walk, reverse direction of genes is allowed in global directed network pathway, and this can increase the probability for the edges to connect the next genes [4].

The group specific tuning parameter is introduced to be implemented in the directed random walk algorithm to identify cancerous genes for higher accuracy in cancer classification of the gene expression data. The directed random walk algorithm identifies genes within pathways, leading to over-fitting. The genes identified by the existing algorithm within pathways are performed in a fixed direction with specific conditional independencies probability at discrete times [5]. The existing algorithm starts a new random walker to generate reproducible pathways for cancerous genes, which then, continue to the neighbouring sites of the genes until no neighbouring sites of the genes exist within the pathways. When the tuning parameter is too small, it can lead to over-fitting for the classifier model.

Besides that, the existing algorithm that identifies the genes within pathways also produces poor discriminating power. The discriminating power denotes the reproducible power and the robustness of pathways, whether the pathways are significantly differentially expressed or not [6]. When the tuning parameter is too large, it can lead to the production of poor discriminating power.

## II. MATERIAL AND METHOD

Genes are the fundamental unit of heredity and the basic structure of DNA. Gene expression data is extracted from human DNA through microarray analysis. Gene expression data is used as input data for the experiment, while the method that applied in this experiment is specific directed random walk which enhances from directed random walk.

### A. Gene Expression Data

The Microarray dataset used in this experiment was downloaded from the National Centre for Biotechnology Information (NCBI). It is GSE10072 for lung adenocarcinoma [7] with 107 samples where 58 samples are cancer samples while 49 are normal samples. These 107 samples are constructed from GSM254625 until GSM254731. This dataset contains 13788 genes and was used to compare with a group of metabolic pathways, which were obtained from the Kyoto Encyclopaedia of Genes and Genomes Databases [8, 9] and further developed into a global pathway network [4]. Pathways obtained and used are listed in Table 1. They are top 20 frequently selected pathway for lung cancer. The frequency of pathway markers for lung cancer classification is listed in Table 2. Global pathway network was formed by 300 graphs which cover 4113 nodes and 40 875 directed edge where the nodes represent the genes and directed edge represents how genes interact and regulate among each other [4].

The lung adenocarcinoma cancer dataset is chosen as the experimental dataset. Two classes of the lung datasets are employed for the sake of comparison. They are the tumour class and normal class. Overall, in the gene expression data, there are 107 samples and 13788 genes [8]. Out of the 13788 genes, 7948 genes have a p-value of less than 0.05, which means 7948 genes are used in the final experiment after filtering process in specific directed random walk (sDRW).

TABLE I  
TOP 20 OF PATHWAYS DATA SELECTED FOR LUNG CANCER  
CLASSIFICATION

No.	Name of Pathways	No. of genes in pathways activity
1	Tight junction	63
2	ECM-receptor interaction	49
3	Focal adhesion	118
4	Leukocyte transendothelial migration	63
5	Pancreatic secretion	45
6	Neuroactive ligand-receptor interaction	41
7	Calcium signaling pathway	75
8	PPAR signaling pathway	34
9	Amoebiasis	60
10	Hepatitis C	63

11	Melanogenesis	47
12	Regulation of actin cytoskeleton	115
13	Bacterial invasion of epithelial cells	47
14	Cardiac muscle contraction	15
15	Neurotrophin signaling pathway	69
16	Chemokine signaling pathway	91
17	Adipocytokine signaling pathway	37
18	Vascular smooth muscle contraction	64
19	Adherens junction	43
20	Ether lipid metabolism	20

TABLE II  
FREQUENTLY SELECTED PATHWAYS MARKERS (TOP 20) FOR CANCER  
CLASSIFICATION

No.	Name of Pathways	Frequency of selected pathway markers
1	ECM-receptor interaction	360/1500
2	Pancreatic secretion	230/1500
3	Focal adhesion	225/1500
4	Calcium signaling pathway	131/1500
5	Neuroactive ligand-receptor interaction	114/1500
6	Leukocyte transendothelial migration	109/1500
7	Tight junction	88/1500
8	PPAR signaling pathway	69/1500
9	Amoebiasis	63/1500
10	Hepatitis C	45/1500
11	Melanogenesis	29/1500
12	Regulation of actin cytoskeleton	24/1500
13	Bacterial invasion of epithelial cells	20/1500
14	Cardiac muscle contraction	16/1500
15	Neurotrophin signaling pathway	13/1500
16	Chemokine signaling pathway	12/1500
17	Adipocytokine signaling pathway	12/1500
18	Vascular smooth muscle contraction	6/1500
19	Adherens junction	6/1500
20	Ether lipid metabolism	5/1500

### B. Directed Random Walk Algorithm (DRW)

The directed random walk (DRW)-based method was initially proposed by Liu et al. (2013). The DRW-based method aimed to mine the topological information of the protein-protein interaction network [4]. To capture the topological information in directed network and infer a more robust pathway activity, a pathway topological information mining method is required [4]. The major challenge for inferring the pathway activity is to identify active pathways that have stronger discriminative power and robustness [4].

The directed random walk was applied to evaluate the topological importance of each gene based on the aforementioned topological information, and this method is performed on a merged global pathway network [4]. Fig. 1 illustrates the overview of the DRW-based method proposed by Liu et al. (2013) to infer pathway activity. Based on Fig. 1, the samples used by the directed random walk based method include the gene expression data and disease related pathway data. Besides that, the directed random walk based method also continues to analyse the samples for inferring pathway activity through the global pathway network (as shown in Fig. 1).

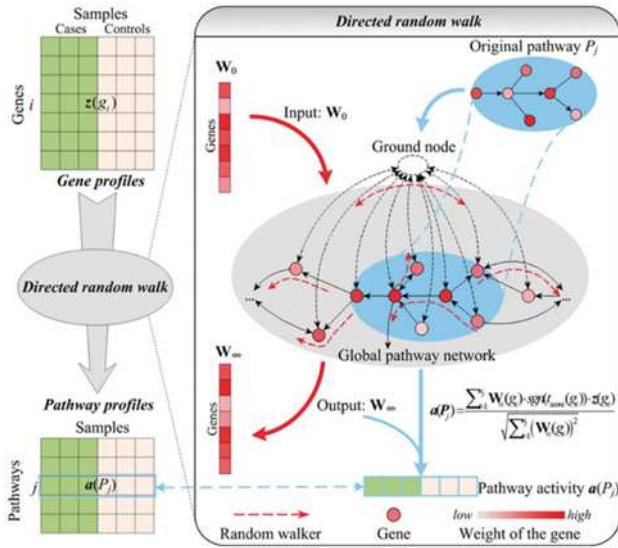


Fig. 1 Overview of directed random walk (DRW)-based method to infer pathway activity [4]

The directed random walk will restart the stimulation of random walker that starts on a source node,  $s$ . The walker transits from its current node to a random neighbouring node or goes back to the source node  $s$  with probability,  $r$ . Formally, the DRW is written as:

$$W_{t+1} = (1 - r)M^T W_t + rW_0 \quad (1)$$

$W_t$  is a vector where the  $Z$ -th element holds the probability of being at node  $z$  at time  $t$ , and  $M$  is the row-normalized adjacency matrix of the graph  $G$ .

The initial probability  $W_0$  was constructed by assigning data to each node by using their  $t$ -test score, after normalizing to a unit vector. The restart probability,  $r$  is set as 0.7, and it will be tuned and further described in the next sub-chapter. Due to the usage of  $t$ -test scores as the initial probability, the magnitude of the  $t$ -test scores also contributed to weight adjustments [4]. Thus, the genes that are both topologically important and significantly differentially expressed will obtain higher weights.

20 Pathway markers are selected to be specific for the cancer classification. This will further discuss in next section, materials.

### C. Specific Directed Random Walk Algorithm (sDRW)

By using directed random walk algorithm, some informative genes may exclude from the pathways, and some uninformative genes may include within the pathways since some of the pathway data are usually gathered from the biological literature [10]. Hence tuning parameter selection method is proposed to integrate into directed random walk algorithm. The tuning parameter selection method is aimed to estimate the nearly optimal parameter for pathways; it is also important to identify an effective predictive model and the significant cancerous genes [9], [6]. Therefore, the tuning parameter selection method can lead to better performance of the directed random walk.

In the directed random walk algorithm, there is 1 tuning parameter, restart probability ( $r$ ), also known as gamma that plays an important role in determining an effective predictive

model [4]. The tuning parameter,  $r$  is applied to estimate the probability of the node to move into the neighbouring nodes or going back to the previous node. With different numbers of restart probability, the specific directed random walk algorithm (sDRW) can list all pathways that are topologically important and significant to cancerous genes. This can lead to reduced miss up of significant pathways and reduce the consumed time by avoiding from using all pathways in the classification [4].

Instead of the general restart probability that implements in the directed random walk, 0.7 [4], additional of 8 different restart probabilities are applied in the specific directed random walk, which are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, and 0.9. The significant genes within pathways can be selected and classified more accurately by using different restart probability.

The procedure consists of three main steps. In Step 1, the genes in microarray data are selected and grouped based on their prior pathway information from the pathway data. This process repeats for each pathway in the pathway data, and there is a possibility that some genes are not involved in any pathways at all. The  $P$ -value of genes is calculated, and the significant level of genes is differentiated accordingly. From this step, the new sets of gene expression data are produced to be evaluated by the sDRW.

After this, the weight,  $t$ -score and reproducible power of pathways are calculated. Table 3 illustrates the procedure of sDRW in pseudo-code. If the reproducibility of a gene is big, this indicates that it has more robustness and more significance to cancer. With this, the pathway that contains the genes will proceed to be evaluated by the restart probability,  $r$  that is also known as the tuning parameter. In the end, specific cancerous genes are identified and being classified accordingly. 5-fold cross validation is used to calculate the classification error [9] while the area under the curve is used to evaluate the performance of the classifier [11], [12]. Higher AUC indicates better accuracy of classification.

TABLE III  
THE PROCESS OF SDRW

<p><b>Algorithm:</b> sDRW  <b>Input:</b> GE, PD, <math>r</math>  <b>Output:</b> SP: Significant pathways  IG: Informative genes</p> <p><b>Begin</b></p> <p><b>For</b> <math>j=1</math> <b>to</b> the max no. of pathways in PD <b>do</b>  Select genes that <b>are</b> significant (<math>p &lt; 0.05</math>); and  remove genes that <b>are</b> not significant (<math>p &gt; 0.05</math>);</p> <p><b>For</b> <math>i = 1</math> <b>to</b> all genes in GE <b>do</b>  Assign <b>the</b> initial weight of genes  with <math>r = (0.1 - 0.9)</math>,  abs (<math>t</math>-test score),  normalized vector;</p> <p><b>End-for</b></p> <p>Calculate <b>the</b> weight of genes;  Sign function for <math>t</math>-test scores of genes;  Calculate <b>the</b> reproducible power for PA;</p>
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**If the** reproducible power of PA  $j > P_{a j+1}$   
 More robustness PA for  $j$ ;  
**End if**

Evaluate pathways;  
 Estimation of  $r$ ;  
**For**  $r = 0.1$  to  $0.9$  **do**  
 $W_{t+1} = (1 - r)M^t W_t + rW_0$ ;  
 Calculate the error rate with  $r$ ;  
**End-for**

Identify genes within PA;  
 Classify the genes based on cancer types;  
 Calculate the classification error with 5-fold CV'  
 Evaluate the classifier by AUC;  
**End For**

**End**

**Legend**  
 GE = Gene Expression Data  
 PD = Pathway Data  
 $r$  = restart probability / tuning parameter  
 abs = absolute  
 $i$  = number of genes  
 $j$  = number of pathways  
 PA = Pathway activity  
 CV = Cross Validation  
 AUC = Area Under Curve

### III. RESULTS AND DISCUSSION

#### A. Results

The tuning parameter is built based on the constant restart probability. To tune the probability and seek for a different result that may be missed, 0.1 – 0.9 of restart probability is used. The usage of this tuning parameter is to specific select the risk-active pathway that significant to lung cancer. Instead of the general restart probability, 0.7 [4], 9 different restart probabilities are applied in the sDRW, which are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9. With this, the significant genes within pathways can be selected and classified more accurately. “√” indicates that the significant pathways are shown after running the tuning parameter in the DRW algorithm.

TABLE IV  
 PATHWAY DETERMINED BY SPECIFIC DIRECTED RANDOM WALK

Pathways	Specific Directed Random Walk (sDRW)								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Tight junction	√								
ECM-receptor interaction		√	√	√	√				
Focal adhesion				√	√		√	√	
Leukocyte transendothelial migration						√			
Pancreatic secretion									√
Calcium signaling pathway									

Neuroactive ligand-receptor interaction									
PPAR signaling pathway									
Amoebiasis									
Hepatitis C									
Melanogenesis									
Regulation of actin cytoskeleton									
Bacterial invasion of epithelial cells									
Cardiac muscle contraction									
Neurotrophin signaling pathway									
Chemokine signaling pathway									
Adipocytokine signaling pathway									
Vascular smooth muscle contraction									
Adherens junction									
Ether lipid metabolism									

TABLE IV  
 PATHWAY DETERMINED BY SPECIFIC DIRECTED RANDOM WALK

and **Error! Not a valid bookmark self-reference.** show the results of identified risk-active pathway with the Specific Directed Random Walk and Directed Random Walk. Results in TABLE IV

PATHWAY DETERMINED BY SPECIFIC DIRECTED RANDOM WALK

show five risk-active pathways that are significant to the lung cancer genes where the restart probability is 0.1 to 0.9 while the directed random walk only can identify 1 risk-active pathway. The five significant pathways that identified by specific directed random walk are a tight junction, ECM-receptor interaction, focal adhesion, leukocyte transendothelial migration, and pancreatic secretion while the only pathway that identified by directed random walk are focal adhesion.

The tight junction displayed positive results at 0.1, the lowest restart probability. Pathway ECM-receptor interaction has shown positive results at the restart probability of 0.2 to 0.5, whereas the Focal adhesion produced positive results are 0.4, 0.5, 0.7 and 0.8 of the restart probability. The Leukocyte transendothelial migration displayed encouraging feedback at the restart probability 0.6 while the Pancreatic section responded to the restart probability of 0.9. This indicates that the ECM-receptor interaction and focal adhesion have the most frequent results generated by the restart probability. This displays that they are much more significant compared

to the other significant. However, this does not mean that they contain more significant genes compared to other significant pathways.

TABLE V  
PATHWAY DETERMINED BY DIRECTED RANDOM WALK

Pathways	Directed Random Walk
	0.7
Tight junction	
ECM-receptor interaction	
Focal adhesion	√
Leukocyte transendothelial migration	
Pancreatic secretion	
Calcium signaling pathway	
Neuroactive ligand-receptor interaction	
PPAR signaling pathway	
Amoebiasis	
Hepatitis C	
Melanogenesis	
Regulation of actin cytoskeleton	
Bacterial invasion of epithelial cells	
Cardiac muscle contraction	
Neurotrophin signaling pathway	
Chemokine signaling pathway	
Adipocytokine signaling pathway	
Vascular smooth muscle contraction	
Adherens junction	
Ether lipid metabolism	

Pathways that showed negative feedback with the restart probability of 0.1 to 0.9 are calcium signaling pathway, neuroactive ligand-receptor interaction, PPAR signaling pathway, Amoebiasis Hepatitis C, melanogenesis, regulation of actin cytoskeleton, bacterial invasion of epithelial cells, cardiac muscle contraction, neurotrophin signaling pathway, chemokine signaling pathway, adipocytokine signaling pathway, vascular smooth muscle contraction, adherens junction, and ether lipid metabolism.

To further demonstrate the restart probability, restart probability is applied in inter-validation. For a fair and effective comparison with other methods, within dataset five-fold cross validation is carried out. To reduce the effect of sensitivity in feature selection while comparing different pathway, only top 50 pathway activities are used [4]. The top 50 pathway activities are ranked by P-values in increasing order as the candidate feature for feature selection [4]. The classifier was built based on logistic regression.

Table 6 shows the average area under the curve (AUC) of each restart probability. Within the dataset, validation is attempted to perform five-fold cross validation. Five-fold

splits of samples in each dataset, four-fifths of the samples were used as the training set to build the classifier, and the remaining one-fifth was used as the test set.

TABLE VI  
CLASSIFICATION PERFORMANCE COMPARISON ON DIFFERENT RESTART PROBABILITY

Restart Probability	Mean AUC
0.1	0.9687
0.2	0.9759
0.3	0.9704
0.4	0.9692
0.5	0.9883
0.6	0.9939
0.7	0.9706
0.8	0.9881
0.9	0.9761

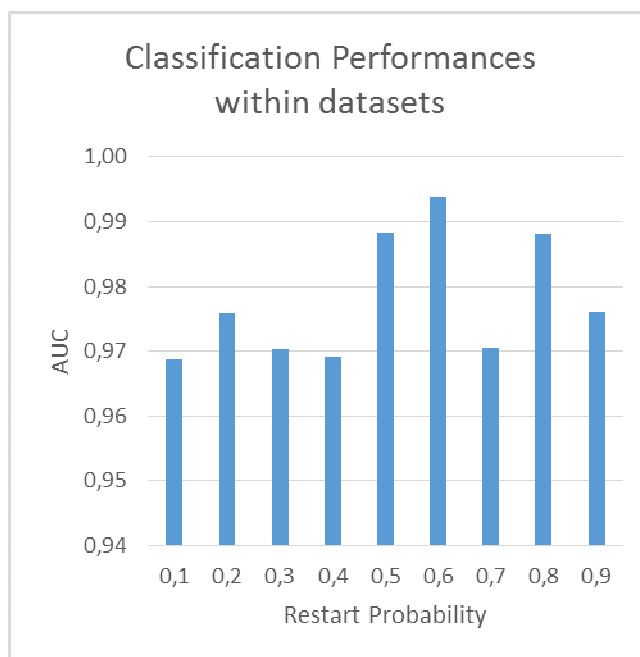


Fig. 2 Classification performances of different restart probability within datasets using logistic regression

Fig. 2 presents a summary of the AUC of the inter-validation experiments. The proposed sDRW method obtained AUCs of restart probability 0.1 (0.9687), 0.2 (0.9759), 0.3 (0.9704), 0.4 (0.9692), 0.5 (0.9883), 0.6 (0.9939), 0.7 (0.9706), 0.8 (0.9881), and 0.9 (0.9761).

The highest accuracy of classification is 0.9939 where restart probability dropped at 0.6. The experiment proved 0.7 is not the best restart probability. This indicates that tuning parameter is needed to define the best restart probability for the datasets. The second and third higher accuracies are 0.9883 (0.5 restart probability) and 0.9881 (0.8 restart probability). Hence, 0.6 will be set as major restart

probability for lung adenocarcinoma cancer, while 0.5 and 0.8 can be used as reference restart probability.

Noted that, restart probability can perform differently per the datasets. The experiment shows that 0.1, 0.3, 0.4 and 0.7 are not suitable to be used as restart probability for lung adenocarcinoma cancer. This is because the accuracy of 0.1, 0.3, 0.4 and 0.7 are between 0.969 to 0.971, which are significantly low compared to restart probability of 0.6.

### B. Discussion

This paper focuses on identifying the significant pathways that are related to gene expression data by proposing the sDRW. From the experiments and analyses, the sDRW shows plenty of pathways that are significant to gene expression data. By comparing the resulted significant pathways to gene expression data, we can easily locate the relevant genes that may be significant to cancerous genes [13].

The sDRW has also shown its ability on resulted pathways by tuning the restart probability. Out of the 20 pathways that are related to lung cancer, only five pathways denote positive results from the algorithm where only 2 major pathways showed higher significance compared to most of the results.

Even with correctly selected pathways, the sDRW may select the uninformative pathways. However, it has narrowed down the selected pathways whereby out of 20 pathways, only five pathways showed higher chances of being significant to lung cancer. This can reduce the time for researchers to figure out the significant genes by using all relevant pathways. This does not mean the other pathways are not significant to lung cancer, but it proves that this unselected pathway is not significant to the gene expression data used in this experiment. The result pathways are used in feature selection as they contain common genes that are significant to the lung tumour.

By tuning the restart probability from a fixed probability, 0.7 to a range of probability, 0.1 – 0.9, the number of resulted pathways increases. This resulted to the pathway that may contain insignificant genes, and this can lead to a low discriminative power. As demonstrated in the results, the restart probabilities of 0.1 and 0.9 have no common results with other restart probabilities. This is because the range of probability from 0.1 to 0.9 is used, and not all are sufficient to identify the significant pathways. When the restart probability is too small, it can lead to over-fitting of the training model and give too little sparse to the produced classifier; and if it is too big, it can lead to under-fitting of the training model, which again can be very sparse to the classifier [14].

The reliable performance of sDRW could be attributed to the strategy of different restart probability. By testing with a range of 0.1 to 0.9 restart probability, the sDRW could identify the best restart probability to cancer. Thus, the implement of specific tuning parameter will increase the accuracy of classification.

Therefore, further research, especially in the tuning parameter selection methods, is needed to surmount the limitation of the sDRW where a process of identifying the useful restart probability is needed as well as other algorithms enhancement [15], [16]. A complete library of

restart probability could help to clarify the suitable restart probability for every cancer type. With the rapid development of human interaction databases, a complete restart probability library will enable a more accurate prediction of cancerous genes which covered most of the cancer type.

### IV. CONCLUSIONS

Directed random walk algorithm had been succeeding improved by implementing tuning parameter selection method. By using different restart probability, different significant pathways are selected and affected the accuracy of classification. Even the accuracy is increased, but the restart probability is only suitable for the sample datasets. Please note that different datasets required different restart probability. Hence, the range of restart probability is proposed.

Therefore, a complete library of restart probability could help to clarify the suitable restart probability for every cancer type. With the rapid development of human interaction databases, a complete restart probability library will enable a more accurate prediction of cancerous genes which covered most of the cancer type. Besides, further research, especially in the tuning parameter selection methods, is needed to surmount the limitation of the sDRW where a process of identifying the useful restart probability is needed.

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