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Chemo-informatics Studies on Natural Occurring Naphthoquinone Coloring Agents.

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ABSTRACT

Similarity studies of natural occurring naphthoquinone coloring agents, lapachol , chinone, chimaphilin, juglon, lawsonia, napthochinone yellow, Spinochrome D using Tanimoto coefficient and Euclidean Distance measurents are reported. C Algorithm and MATLAB Algorithm are developed for calculating the Tanimoto coefficient and Euclidean Distance values of coloring agents. The values of Tanimoto coefficient and Euclidean Distance obtained using both the algorithm are found to be same. Results shows that the compound Juglon and 5 Lawsonia have highest similarity with Tanimoto coefficient ,0.6 and Euclidean Distance , 1.414 and Chimaphilin has quite good similarity with Spinochrome D with Tanimoto coefficient .5714 and Euclidean Distance , 1.732. Lapachol and 2 Chinone also show good similarity with Tanimoto coefficient .5455 and Euclidean Distance , 2.236. Interestingly Napthochinone yellow and Chinone, have lowest similarity with Tanimoto coefficient 0.25 and Euclidean distance of 2.449. But both the compounds have good similarity Juglon and Lawsonia with Tanimoto coefficient 0.5 and Euclidean distance values of 1.41 and 2.0 respectively

Keywords: Tanimoto coefficient, Euclidean Distance, Naphthoquinone coloring agents, C Algorithm , MATLAB Algorithm.

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INTRODUCTION

The applications of information technology have given birth to different disciplines namely, Bioinformatics, Chemoinformatics, Geoinformatics, Health informatics, Laboratory informatics, Neuroinformatics, Social informatics. The term "Chemo informatics" appeared a few years ago and rapidly gained widespread use. The use of information technology and management has become a critical part of the drug discovery process as well as to solve the chemical problems. The chemoinformatics is a generic term that encompasses the design, creation, organization, management, retrieval, analysis, dissemination, visualization, and use of chemical information. The transformation of data into information and information into knowledge is an endeavor needed in any branch of chemistry, not only in drug design [1]. Chemo-informatics is a novel discipline dedicated to the storage, management, analysis, dissemination and usage of chemical information [2,3]. With aims to “mix information resources to transform data into information, and information into knowledge”, chemoinformatics will facilitate and accelerate the pace of lead discovery and optimization [2]. Chemoinformatics has effectively assimilated the knowledge of mathematical statistics, computer and information science and has gradually generated three major study objects, *i.e.*, computer-aided structure determination, computer-aided molecular design and computer-aided synthesis [4-8]. The study of relationship between molecular structure and molecular function or reactivity of the substances (in particularly of the organic compounds) is integral to chemistry.

According to similar property principle [9] the “structurally similar molecules tend to have similar properties and similar molecules exert similar biological activities". Medicinal chemists have made use of this concept to modify the structures of biologically active compounds. However, similarity and diversity of chemical structures cannot be defined in an objective manner. Several structure-activity relationships studies demonstrate that chemically similar compounds may have significantly different physico-chemical properties [10-13]. Sometimes, similar organic structured molecules may even have opposite function or activity. Molecular similarity can be calculated structurally or evaluated based on molecular properties , biological activities, shapes and 3D molecular fields, *etc*. Tanimoto coefficient is the most widely used criterion in molecular similarity measurement. Usually, if two molecules have a Tanimoto coefficient of > 0.85, they are regarded as structurally similar [14].

In this paper we describe Chemoinformatics studies on natural occurring napthoquinone coloring agents such as lapachol , chinone, chimaphilin, juglon, lawsonia, napthochinone yellow, Spinochrome D. The origin of these natural occurring napthoquinone coloring agents varies from roots to leaves to nuts. The napthoquinone coloring agents are found to be present in various sea urchins [15]. Lapachol from alkannin is a red alkanin colorant for cosmetic and food . Alkanet in an ancient dye stuff known throught Europe. Alkanet root contains red colouring matter –anchusin. Lapachol yellow from tropic wood. Chinone(Lapachol) is yellow crystalline material from heart wood. Chimaphilin is a yellow naphthoquinone which occurs naturally in various chimaphila and Pyrola species. In Chimaphila umbellata (winter green) and C. maculata, it is a major constituent. Folk medicine recommends the leaves of Chimaphila species as a topical application to treat skin diseases. Since 1887, winter green is claimed to have caused dermatitis and to have been responsible for "idiosyncrasy". Experimental sensitization using the open epicutaneous as well as Freund's complete adjuvant technique has now revealed that chimaphilin is a moderate contact sensitizer [26]. Juglon (Butter nut , P.Walnut, Black Walnut) is hulls of nut containing dark colorant, which is used as pink brown to dark brown. Lawsonia is a powder from grinded dry leaves and sprouts of heena brush Lawsonia. Naphthochinone yellow is a yellow color dye. Spinochrome D is from sea urchins [15]. Several plant dyes are rich in naphthoquinones such as lowsone from henna , juglone from , walnut and lapachol from alkanet reported to exhibit antibacterial and antifungal activity. Recently these dyes have been used to make clothing antibacterial. Natural along with natural fabrics are protective to skin. This can improve human’s body aura along with inhibition of bacterial growth due to sweat and other reasons. The textiles dyed with natural dyes can be very useful in developing clothing for infants , elderly and infirm people to protect them against common infections. They will be equally useful in bed linen , carpet and other home textile which are major propagation of common infections [16, 17]. Antimicrobial Activities of the henna extract and some synthetic naphthoquinones derivatives have recently been reported [18]. Because of the recent interest in dying fabrics with natural dyes , dying parameters of hydroxynaphthoquinones extract from Arnebia nobilis Rech have recently been reported [19]. The chemoinformatics similarity studies will help us to understand the evolution of

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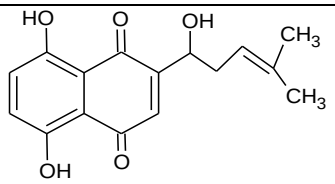
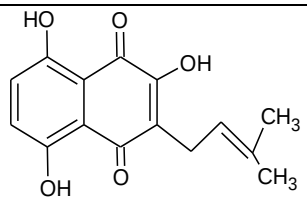
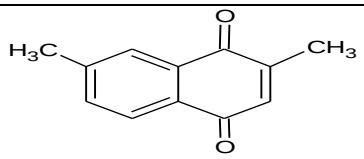
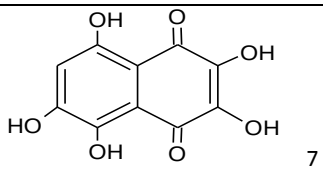
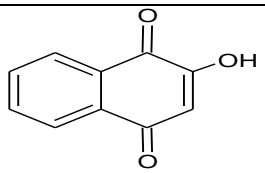
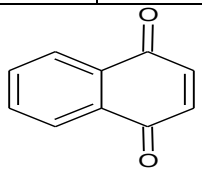
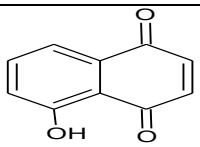
naphthoquinone coloring agents in nature as well as their structure function relationship. This similarity study on natural occurring naphthaquinone coloring agents will also be useful in adjusting the hue of the fabric.

MATERIAL AND METHODS

The structure of the organic were taken from Chem Spider and other internet sources (Table-1). The molecules were decomposed off manually (Table-2).

Table 1 : Structures of Naphthoquinones

 1 Lapachol	 2 Chinone	 3 Chimaphilin
 7 Spinochrome D	 5 Lawsonia	 6 Napthochinone yellow	 4 Juglon

Tanimoto coefficient Measurement

The structure of the substances to be compared is decomposed into fragments and the structural fragments or features that are present in the given molecule are turned ON (set as 1) and the ones that are absent are kept OFF (set as 0) [20-22]. Thus, for each molecule one ends up having a string containing "1"s and "0"s (bit string) as determined by the elements of the dictionary. Bits are set only once irrespective of the frequency of occurrence of the given key. Bits get set on the basis of fragments of whole structure and there is poor capturing of properties of the whole molecule. The structures [23] of seven natural occurring napthoquinone coloring agents such as alkanet, chinone, chimaphilin, juglon, lawsonia, napthochinone yellow, Spinochrome D, under consideration (Table-1) are decomposed into smaller fragments and a dictionary of all the fragments was prepared (Table-2,Column – 1, structure of the fragments).

The fragments present in the dictionary are matched with fragments of the individual naphthoquinone coloring agent . If the fragment of the naphthoquinone coloring agent matches with the fragment present in the dictionary, it is given the value of "1 "and the fragment that is absent is given the value of "0" This way a bit- string finger print of each naphthoquinone coloring agent is prepared (Table-2). Once bit-strings finger print is ready, any of the association coefficients can be used to find out the similarity between any two given molecules. Tanimoto coefficient is a widely used to determined the similarity based on fingerprints (bit-string representations). The Tanimoto coefficient is determined by comparing two molecules A and B bit – string fingerprints using the equation given below. For an example, If N1 is number of features (ON bits) in 1, N2 is the number of features (ON bits) in 2, and N12 is the number of features (ON bits) common to both 1 and 2, then, Tanimoto coefficient simply is: $\tau = N12 / N1 + N2 - N12$

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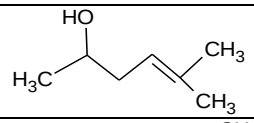
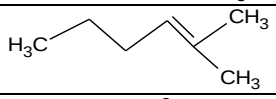
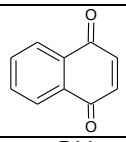
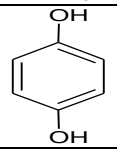
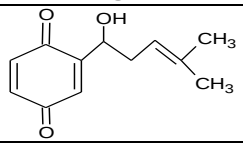
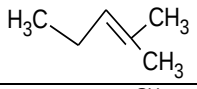
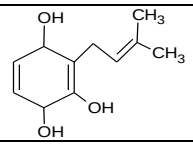
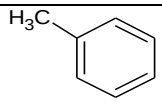
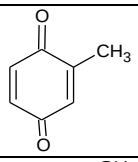
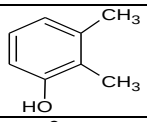
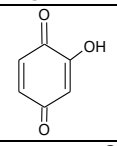
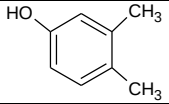
Table 2: Library of Naphthoquinones Structures Fragments

Fragments	1	2	3	4	5	6	7
-OH	1	1	0	1	1	0	1
	1	0	0	0	0	0	0
	1	0	0	0	0	0	0
	1	1	1	1	1	1	1
	1	1	0	0	0	0	0
	1	0	0	0	0	0	0
	1	1	0	0	0	0	0
	0	1	0	0	0	0	0
CH_4	0	0	1	0	0	0	1
	0	0	1	0	0	0	0
	0	0	1	0	0	0	1
	1	1	0	1	0	0	0
	0	1	0	0	1	0	0
	0	0	0	0	0	0	1
	1	1	1	1	1	1	1

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Euclidean Distance

Euclidean Distance (ED) measurement is Pythagorean distance and has binary dimensions, equivalent to the square root of the Hamming distance (i.e., square root of the number of bits that are different). Os are treated as significant. Smaller values mean more similarity [22].

Example:

↓ ↓
1101**1**0**0**0
1101**0**0**1**0
x x
ED=√2

We have determined similarity between natural occurring naphthoquinone coloring agents using Tanimoto coefficient and Euclidean Distance. To calculate similarity coefficients algorithm using C[24] and MATLAB [25] were applied The detail of both the algorithms is given below.

C Algorithm for Tanimoto coefficient and Euclidean Distance

Array(a[i][j],i,j)
a[i][j]: Array in which data is stored.
i:Number of rows.
j:Number of columns.
Tanimoto Coefficient (t,k,l,o,tc)
t: Number of ON bits common to v and y.
k: Number of ON bits in v.
l: Number of ON bits in y.
o: Equal to the relation l+k-t.
tc: Tanimoto Coefficient.
v:Reference Number.
y:Reference Number.
Euclidean Distance(g, sqrt(g))
v:Reference Number.
y:Reference Number.
g: Number of bits that are different.
sqrt(g): Euclidean Distance.
1.Start
2.Print " Array,a[i][j]".
3.Input the Reference number of the ____ from the list. <---------{v, Reference number}
4. If a[i][v-1]==1
The number of ON bits present in 'v' are calculated. <------------{k,Number of ON bits in v}
5.Print "Number of ON bits in v: ".
6.Input the Reference number of the _____form the list. <-----------{y, Reference number}
7.If a[i][y-1]==1
The number of ON bits present in 'y' are calculated. <------------{l,Number of ON bits in y}
8.Print "Number of ON bits in y: ".
9. If a[i][v-1]==1 && a[i][y-1]==1
The number of ON bits common to 'v' and 'y' are calculated. <--------{t,Number of ON bits common to v and y}
10.Print "Number of ON bits common to v and y: ".
11.Compute the relations o=l+k-t and tc=t/o. <-----------{tc,: Tanimoto Coefficient}
12.Print"Tanimoto Coefficient: ".
13.If (a[i][v-1]==0 && a[i][y-1]==1)|| (a[i][v-1]==1 && a[i][y-1]==0)

The number of bits that are different are calculated.<----------{g,number of bits that are different}
14.Print"Euclidean Distance".
15.Exit

C program Codes

```
#include<stdio.h>
#include<conio.h>
#include<math.h>
void main()
{
inti,k=0,j,p,v,y,l=0,z,t=0;
doubletc,o,g=0;
int
a[15][7]={1,1,0,1,1,0,1,1,0,0,0,0,0,0,1,0,0,0,0,0,0,1,1,1,1,1,1,1,1,1,0,0,0,0,0,1,0,0,0,0,0,0,1,1,0,0,0,0,0,0,1,0,0,0,0,0,
0,0,1,0,0,0,1,0,0,1,0,0,0,0,0,0,0,1,0,0,0,1,{1,1,0,1,0,0,0},0,1,0,0,1,0,0,0,0,0,0,0,0,1,1,1,1,1,1,1,1};
clrscr();
for(i=0;i<15;i++)
{
for(j=0;j<7;j++)
printf("%2d",a[i][j]);   printf("\n");
}
printf("\n1.\n2.\n3.\n4.\n5.\n6.\n7.\n");
printf("First Choice: ");
scanf("%d",&v);
switch(v)
{
case 1:
{
for(p=0;p<15;p++)
if(a[p][0]==1)
k++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",k);
break;
case 2:
{
for(p=0;p<15;p++)
if(a[p][1]==1)
k++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",k);
break;
case 3:
{
for(p=0;p<15;p++)
if(a[p][2]==1)
k++;
    }
printf("\n");
```

```
printf("No. of features(ON Bits): %d",k);
break;
case 4:
{
for(p=0;p<15;p++)
if(a[p][3]==1)
k++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",k);
break;
case 5:
{
for(p=0;p<15;p++)
if(a[p][4]==1)
k++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",k);
break;
case 6:
{
for(p=0;p<15;p++)
if(a[p][5]==1)
k++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",k);
break;
case 7:
{
for(p=0;p<15;p++)
if(a[p][6]==1)
k++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",k);
break;
default:
printf("Invalid");
 }
printf("\n");
printf("Second Choice: ");
scanf("%d",&y);
switch(y)
{
case 1:
{
for(p=0;p<15;p++)
if(a[p][0]==1)
l++;
    }
```

```
printf("\n");
printf("No. of features(ON Bits): %d",l);
break;
case 2:
{
for(p=0;p<15;p++)
if(a[p][1]==1)
l++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",l);
break;
case 3:
{
for(p=0;p<15;p++)
if(a[p][2]==1)
l++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",l);
break;
case 4:
{
for(p=0;p<15;p++)
if(a[p][3]==1)
l++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",l);
break;
case 5:
{
for(p=0;p<15;p++)
if(a[p][4]==1)
l++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",l);
break;
case 6:
{
for(p=0;p<15;p++)
if(a[p][5]==1)
l++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",l);
break;
case 7:
{
for(p=0;p<15;p++)
if(a[p][6]==1)
```

```
l++;
    }
printf("\n");
printf("No. of features(ON Bits): %d",l);
break;
default:
printf("Invalid");
}  printf("\n");
  {
printf("\nNo. of features (ON Bits) common to both: ");
   }
{
for(z=0;z<15;z++)
if(a[z][v-1]==1)
if(a[z][y-1]==1)
t++;
printf("%d\n",t);
o=l+k-t;
tc= t/o;
printf("\nTanimotoCoefficent: %f",tc);
 }
  {
for(i=0;i<15;i++)
 if(a[i][v-1]==0 && a[i][y-1]==1 || a[i][v-1]==1 && a[i][y-1]==0)
g++;
printf("\n");
printf("Euclidean Distance: %2.3f ",sqrt(g));
  }
getch();
}
```

MATLAB Algorithm for calculating Tanimoto coefficient

TC was calculated by a program code implemented in MATLAB R2012b (http://www.mathworks.com/). Various steps of the code are given in the form of detailed algorithm:

Let x and y are fingerprints of two drugs which are to be tested for similarity. Let V be the values, each fingerprint, i.e., x and y take:

where V →{0,1}

Step 1: Define a function 'Calculate _Tanimoto (x,y)' , where x and y are arrays in nature and are fingerprints of two drugs whose similarity is to be tested. The length of both the arrays should be same.

Step 2: Calculate x & y and store the result in a temporary array T_1 where & is logical AND operator. AND operator output is ON(1) if both input bits are ON(1), if neither or only one input bit is ON(1), the output is OFF(0). Since x,y are in the form of arrays of same length, both are traversed sequentially in order to check each bit pair.

Step 3: Calculate number of ON(1) bits in T_1 (calculated in step 2). The result will be stored in N_{xy} , which is the measure of number of ON(1) bits common to x and y.

Step 4: Calculate number of ON(1) bits in array 'x' , store the result in N_x .

Step 5: Calculate number of ON(1) bits in array 'y' , store the result in N_y .

Step 6: Compute the relation $N_{xy} / (N_x + N_y - N_{xy})$ and store the result in variable TC.

Step 7: Return TC.
TC is Tanimoto Coefficient for two drugs having x and y as their fingerprints, respectively. Let V_{TC} be the value, what TC can take, then $V_{TC} \rightarrow [0,1]$
For two exactly similar drugs the value of TC will be one(1).
The function 'Calculate_Tanimoto(x,y)' defined in Step 1 can be called to calculate value of TC of any two natural products by passing their corresponding fingerprint arrays as input parameter.

MATLAB Algorithm for calculating Euclidean Distance

ED is calculated by a program code implemented in MATLAB R2012b. Various steps of the program code are given in the form of algortihm with details:

Let x and y are fingerprints of two drugs which are to be tested for similarity. Let V be the values, each fingerprint, i.e., x and y can take,

where $V \rightarrow \{0,1\}$

Step 1: Define a function 'Calculate _Euclidean (x,y)' , where x and y are arrays in nature and are fingerprints of two drugs whose similarity is to be tested. The length of both the arrays should be same.
Step 2: Calculate xor(x,y) and store the result in a temporary array E_1 where xor() function is logical XOR operator. An XOR operator takes two bits at a time as input and checks if abit has changed or not, a bit can change from 1 to 0 or 0 to 1. It outputs ON(1), if one and only one of the input bits is ON(1). If both the input bits are OFF(0) or both are ON(1), it outputs OFF(0). Since both x and y are arrays of bits, they are traversed sequentially in order to check each bit pait.
Step 3: Calculate number of ON(1) bits in E_1(calculated in step 2). The result will be stored in E_2 , which is the measure of number of times a bit changes in x and y taken together.
Step 4: Compute the square root of E_2 (calculated in step 3) and store the result in variable ED.
Step 5: Return ED.
ED is Euclidean Distance for two drugs having x and y as their fingerprints, respectively.
For two exactly similar drugs the value of ED will be zero (0).
The function 'Calculate_Euclidean (x,y)' defined in Step 1 can be called to calculate value of ED of any two natural products by passing their corresponding fingerprint arrays as input parameter

Matlab Program Code

```
function TC= Calculate_Tanimoto(x,y);
evalin('base','save myvars.mat');
load myvars.mat;
T1=x&y;
Nxy=nnz(T1);
Nx=nnz(x);
Ny=nnz(y);
TC=Nxy/(Nx+Ny-Nxy);
display(TC);
Calculate_Euclidean(x,y);
end
function ED=Calculate_Euclidean(x,y)
E1= xor(x,y);
E2=nnz(E1);
ED=sqrt(E2)
end
```

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RESULTS AND DISCUSSION

The Tanimoto coefficient and Euclidean Distance measurements done using C Algorithm are listed in Table-3and Table-5. The Tanimoto coefficient and Euclidean Distance measurements done using MATLAB Algorithm are listed in Table-4 and Table-6. The values of Tanimoto coefficient and Euclidean Distance obtained using C Algorithm and MATLAB Algorithm are exactly matching. Results shows that the compound 4, (Juglon) and 5 (Lawsonia) have highest similarity with Tanimoto coefficient ,.6 and Euclidean Distance , 1.414. Surprisingly , the compound 3 , (Chimaphilin) has quite good similarity with compound , 7, (Spinochrome D) with Tanimoto coefficient .5714 and Euclidean Distance , 1.732. The compounds 1 (Lapachol) and 2 (Chinone) also show good similarity with Tanimoto coefficient .5455 and Euclidean Distance , 2.236. Interesting feature of this study is that the compound 6 , Napthochinone yellow and compound 2, Chinone, have lowest similarity with Tanimoto coefficient 0.25 and Euclidean distance of 2.449. But both the compounds have good similarity with compounds 4, Juglon and 5 , Lawsonia with Tanimoto coefficient 0.5 and Euclidean distance values of 1.41 and 2.0 respectively. Our results show that the other pairs of compounds possess low similarity.

Table 3 : Tanimoto coefficient Measurement using C algorithm

0	1	2	3	4	5	6	7
1	1	0.5455	0.1667	0.4444	0.3	0.2222	0.25
2	0.5455	1	0.1818	0.5	0.5	0.25	0.2727
3	0.1667	0.1818	1	0.2857	0.2857	0.4	0.5714
4	0.4444	0.5	0.2857	1	0.6	0.5	0.4285
5	0.3	0.5	0.2857	0.6	1	0.5	0.4285
6	0.2222	0.25	0.4	0.5	0.5	1	0.3333
7	0.25	0.2727	0.5714	0.4285	0.4285	0.3333	1

Table 4: Tanimoto coefficient Measurement using MATLAB Algorithm

0	1	2	3	4	5	6	7
1	1	0.5455	0.1667	0.4444	0.3	0.2222	0.25
2	0.5455	1	0.1818	0.5	0.5	0.25	0.2727
3	0.1667	0.1818	1	0.2857	0.2857	0.4	0.5714
4	0.4444	0.5	0.2857	1	0.6	0.5	0.4285
5	0.3	0.5	0.2857	0.6	1	0.5	0.4285
6	0.2222	0.25	0.4	0.5	0.5	1	0.3333
7	0.25	0.2727	0.5714	0.4285	0.4285	0.3333	1

Table 5: Euclidean Distance (ED) measurement using C algorithm

0	1	2	3	4	5		7
1	0	2.236	3.162	2.236	2.646	2.646	3
2	2.236	0	3	2	2	2.449	2.828
3	3.162	3	0	2.236	2.236	1.732	1.732
4	2.236	2	2.236	0	1.414	1.414	2
5	2.646	2	2.236	1.414	0	1.414	2
6	2.646	2.449	1.732	1.414	1.414	0	2
7	3	2.828	1.732	2	2	2	0

Table 6: Euclidean Distance (ED) measurement using MATLAB Algorithm

0	1	2	3	4	5	6	7
1	0	2.236	3.162	2.236	2.646	2.646	3
2	2.236	0	3	2	2	2.449	2.828
3	3.162	3	0	2.236	2.236	1.732	1.732
4	2.236	2	2.236	0	1.414	1.414	2
5	2.646	2	2.236	1.414	0	1.414	2
6	2.646	2.449	1.732	1.414	1.414	0	2
7	3	2.828	1.732	2	2	2	0

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