

Mathematical Modeling and Classification of Viruses from Herpesvirus Family

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ABSTRACT

The process of modeling and classifications of viruses that belong to a specific family is an important for biologist and for many biological applications. There are many ways for Viruses families' classification. The degree of similarity or diversity among the structure of the viruses capsid proteins is very useful in studying the Viruses families' classification and their genetic evolution. It also important propose if we construct a mathematical model of the virus life cycle to be able to fully understand the life cycle of Viruses families' activities. In this paper we introduce a proposed mathematical model for some Herpesvirus family viruses simple life cycle and comprehensive study for its classification using sequence alignment algorithms in order to demonstrate their genetic evolution according to the structure of their capsid protein. Herpesvirus family is considered one of the most important family in the families of the enveloped DNA viruses as it contain many dangerous viruses for human health. This family contain one of newly discovered viruses called Epstein–Barr virus (EBV), also called human herpesvirus 4 (HHV-4), which is one of the most common viruses in human. Infection with EBV occurs by the oral transfer of saliva [1] and genital secretions.

Keywords

Pairwise global alignment, multiple sequence alignment, dot plot matrix, herpesvirus family, phylogenetic tree, MatLab, Phylogenetic.

1. INTRODUCTION TO VIRUSES

Viruses are small infectious agents, but it considers the most dangerous infectious agents for eukaryotic organisms. It can replicates only using living cells of the other organisms. Viruses can multiply in living cells. Viruses once enter a host cell they introduce their genetic material, DNA or RNA, inside the host cell. Viruses have a wide range of host cells for infection ranging prokaryotic (e.g. Bacteria or Eukaryotic (e.g. Plants, Animals, Human, ect..)) . A virus has simple structure where it consist of only two components as shown in Fig 1

1. **Genome:** the genome of viruses is either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA); it contains only one type.
2. **Coat or capsid protein:** it is the protein that encloses the genome.

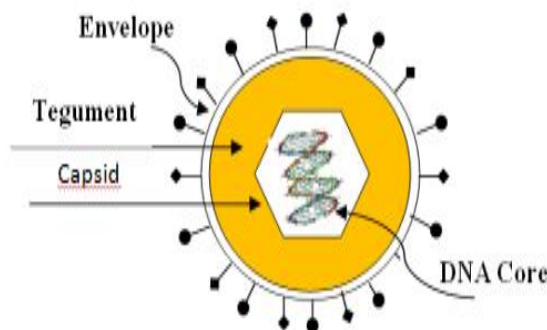


Fig 1: Virus Structure components

Viruses can be classify according to the genome into DNA viruses and RNA viruses.

DNA viruses have the following structures [2]:

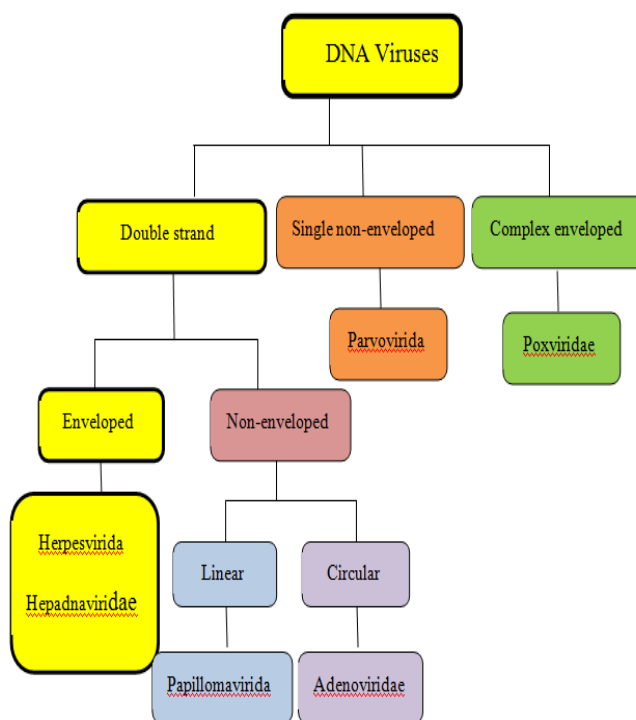


Fig 2: General DNA Virus structure

Our study focuses on enveloped DNA viruses.

1.1. Enveloped DNA Viruses

Enveloped DNA viruses are found in three families [3] as shown in Fig 2 :

1. Herpesviridae (Herpesviruse) family
2. Poxviridae (Boxviruse) family
3. Hepadnaviridae (Hepadnaviruse) family

In this study we will focus on the first family of enveloped DNA viruses which is herpesviruse family colored in yellow, where we will propose a mathematical model for its life cycle and also we introduce a comprehensive study to classify Herpes-virus family members according to the structure of their capsid protein by use different sequence alignment algorithms.

1.2. Herpesviridae Family

Herpesviridae family of viruses comprises enveloped double strand DNA viruses that causes diseases in animals, including humans. Viruses in this family have a double-stranded linear molecular structure with icosahedra symmetry [4][5][6]. Members of this family is known as herpesviruses. The word herpesviruses is derived from the Greek word herpein which refers to the latent and recurring infections phenotype of this family of viruses. This family of viruses contains five species of Herpesviridae which considered dangerous health factor for human health. For instance, HSV-1 and HSV-2 (both of which can cause orolabial herpes and genital herpes), Varicella zoster virus (which causes chicken-pox and shingles), Epstein-Barr virus (which causes mononucleosis) and Cytomegalovirus all of which are considered extremely widespread among humans. There are many reports indicated that at least one of these viruses is infecting 90% , and a latent form of the virus remains in most people [7][8][9]. This family includes eight human pathogens:

- Herpes simplex viruses (HSV) types 1 and 2.
- Varicella-zoster virus (VZV).
- Epstein-Barr virus (EBV).
- Human cytomegalovirus (CMV).
- Human herpes viruses (HHV) types 6,7, and 8.

There are more than 130 known herpesviruses [10], and some are isolated from many organisms such as mammals, birds, fish, reptiles, amphibians, and mollusks [11].

Herpesvirus family contains the following viruses types:-

1. Herpes simplex1 (HSV1)
2. Herpes simplex2 (HSV2)
3. Epstein-barr virus (EBV) or (HHV4)
4. Human herpesvirus6 (HHV6)
5. Human herpesvirus7 (HHV7)
6. Human herpesvirus8 (HHV8)
7. Varicella-zoster virus (VZV)or (HHV3)
8. Human cytomegalovirus (HCMV) or (HHV5)

In this article we will try to classify these viruses according to their capsid protein sequences structure using MatLab algorithms to understand the genetic evolution And the phylogenetic relation of those families.

2. BIOLOGICAL DATA USED IN THIS STUDY

All biological data used (which represents the sequences of the capsid protein of the herpesvirus family) was obtained from the protein sequences repository of the national center for biotechnology information (NCBI) and the UniProt Knowledgebase (UniProtKB) which is the central hub for the collection of functional information on proteins. All these data is

written in FASTA format which is the most popular format types used in writing sequence for bioinformatics applications, and it is a common format in most biological data bases.

3. MATHEMATICAL MODELING OF HERPESVIRUS FAMILY LIFE CYCLE

In this study, we will describe a mathematical model for the herpesviruses virus general life cycles uses the host cell's organelles to replicates new Viruses, which known as Lytic cycle [12]. During this cycle the virus has to infect the cell, So that, the virus attaches itself to the outer cell wall and releases enzymes that weaken the cell wall as shown in Fig 3.

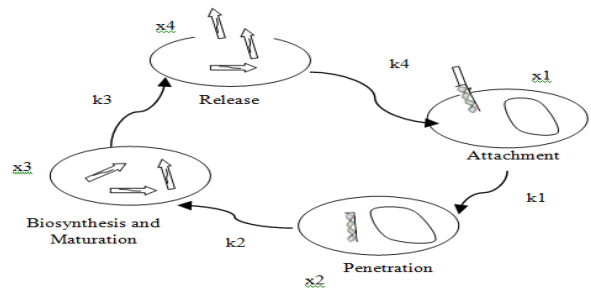


Fig 3: Simple diagram represent herpesviruses Lytic Cycle

The lytic cycle is considered the main cycle in viral replication. As shown in Fig .3, the viral DNA enters the cell and it transcribes itself into the host cell's messenger RNAs and uses them to direct the ribosomes to produce viruses proteins including the capsid protein. The virus takes over the cell's metabolic activities and the host cell's DNA is destroyed . The virus produces progeny phages using the cell energy for its own propagation.. The viruses multiply and the original viruses releases enzymes to break the cell wall. The cell wall bursts, in a process known as lysing. Thus, the new viruses are released [13].

The lytic cycle of a virus consists of six steps [14]. The first two stages, called adsorption and penetration.. In the adsorption stage, the virus must attaches to a receptor on the cell membrane to be able to enter the cell through the plasma membrane.. In the penetration stage, the virus releases its genetic materials into the cell. This is followed by the integration stage in which the host cell gene expression is arrested, and viral materials are embedded into the host cell nucleus The fourth stage is biosynthesis that the virus uses the cell machinery to make large amount of viral components, and at the meantime, destroys the host's DNA. The last two stages, maturation and lysis where the mature virus particles are formed and released .

In this paper, the basic mathematical model for lytic cycle is proposed in four main stages The model of a lytic cycle is converted into a system of equations. The solution of the equations are solved numerically and described how the lytic phage terminates its infection and breach its host's cell envelope over time t.

Then, the reaction scheme is described in the following four reactions as follows:

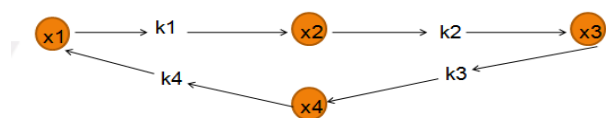


Table 1: This table shows the modeling steps symbols

d/dt	decay	forward	forward	reverse
[x1]	-k1[x1]	0	0	k4[x4]
[x2]	k1[x1]	-k2[x2]	0	0
[x3]	0	k2[x2]	-k3[x3]	0
[x4]	0	0	k3[x3]	-k4[x4]

The dynamics of the system can be written as the following set of first order ODEs:

$$\begin{aligned} d[x1]/dt &= k_4[x4] - k_1[x1], \\ d[x2]/dt &= k_1[x1] - k_2[x2], \\ d[x3]/dt &= k_2[x2] - k_3[x3], \\ d[x4]/dt &= k_3[x3] - k_4[x4]. \end{aligned}$$

This set of ODEs can be numerically solved by using Matlab program. The numerical solution is computed for some initial values and using ODE45 is given below:

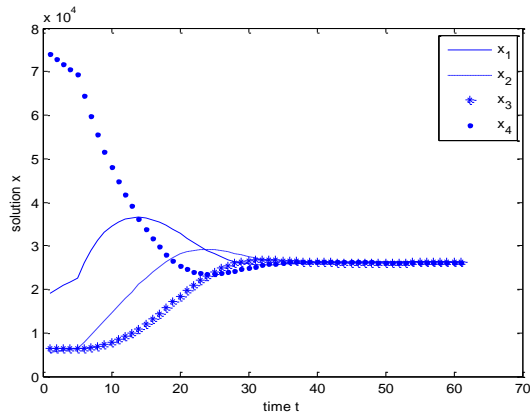


Fig 4: The solution to system of equations produced by ODE45

4. SEQUENCE ALIGNMENT ALGORITHMS

Pairwise global alignment algorithms are intended for comparing two sequences. A dynamic programming (DP) algorithm called Needleman and Wunsch [15] was proposed for pairwise global alignment. Those methods are very useful in analysis of DNA and protein sequences [16, 17]. Many new phylogenetic programs were developed based on those algorithms [18]. There are other dynamic programming algorithms for pairwise global alignment such as Huang and Chao [19] and NGILA [20]. In addition, there are other algorithms for making pairwise local alignment such as the algorithm introduced by Smith and Michael Waterman [21] and to make multiple sequence alignment MSA [22]. The algorithm which was introduced by Thompson et al. to make multiple sequence alignment depends on the progressive alignment. This can be done by constructing a succession of pairwise alignments. Initially, two sequences are chosen and aligned by standard pairwise alignment; this alignment is fixed. Then, a third sequence is chosen and aligned to the first alignment and this process is iterated until all sequences have been aligned. The advantage of progressive alignment is that it is fast and efficient, and in many cases the resulting alignments are reasonable [17,22].

5. PAIRWISE GLOBAL ALIGNMENT (NEEDLEMAN AND CHRISTIAN WUNSCH ALGORITHM)

In our work we use Needleman and Christian Wunsch algorithm to make pairwise global alignment. This algorithm can be summarized as follows:

1. First we consider any two strings such as

$$A = a_i \quad i=1,2,\dots,n$$

$$B = b_j \quad j=1,2,\dots,m$$
2. Scoring matrix of size (n+1)*(m+1) is constructed and initialized using a substitution matrix, e.g., PAM (Percent Accepted Mutations) [23], or BLOSUM (Blocks Substitution Matrix) [24].

$$s(a_i, b_j) = \begin{cases} +1 & \text{if } a_i = b_j, \\ -\mu \leq 0 & \text{if } a_i \neq b_j, \\ -\delta \leq 0 \text{ (for indels)} & \text{if } a_i = -1 \text{ or } b_j = -1. \end{cases} \quad (1)$$

$-\mu$ and $-\delta$ refer to the score of mismatch and *indel* respectively.

Indel means insertions or deletions and it can be represented by using the symbol "-".

4. The best alignment is that produces the largest score for $S_{i,j}$:

$$S_{i,j} = \max \begin{cases} S_{i-1,j-1} + s(a_i, b_j) \\ S_{i-1,j} - \delta \\ S_{i,j-1} - \delta \end{cases} \quad (2)$$

5. The score for elements in the first row and column of the alignment matrix are given by

$$S_{i,0} = -i\delta, \quad S_{0,j} = -j\delta \quad (3)$$

6. The score for the best global alignment of A with B is $S(A, B) = S_{n,m}$, and it corresponds to the highest-scoring path through the matrix and ending at element (n, m). It is determined by tracing back element by element along the path that yielded the maximum score into each matrix element. This algorithm has time complexity $O(nm)$.

This algorithm can be briefly summarized as in the following pseudo code:

```

Global alignment
Input sequences A, B
Set  $S_{i,0} \leftarrow -\delta i$  for all i
Set  $S_{0,j} \leftarrow -\delta j$  for all j
For i=1 to n
    J=1 to m
         $S_{i,j} \leftarrow \max\{S_{i-1,j} - \delta, S_{i-1,j-1} + s(a_i, b_j), S_{i,j-1} - \delta\}$ 
    end
end
    
```

6. DOT-MATRIX OR DOT PLOT METHOD

Dot matrix or dot plot is an important concept for aligning two sequences.

For example if we have the following two sequences

$$s_1 = \text{ccgtaaagat}$$

$$s_2 = \text{gtgtcaagctaactc}$$

The dot matrix for aligning s_1 and s_2 can be constructed as follow:

First we construct a rectangular $n \times m$ matrix such that the rows corresponding to the characters in the first string s_1 and columns corresponding to the characters in the second string s_2 , also the order of characters in s_1 is to the right and is to down in s_2 .

Second a dot is placed in each matrix entry, where a base from s_1 matches a base from s_2 .

Dot matrix of aligning s_1 and s_2 is shown in Fig 5 .

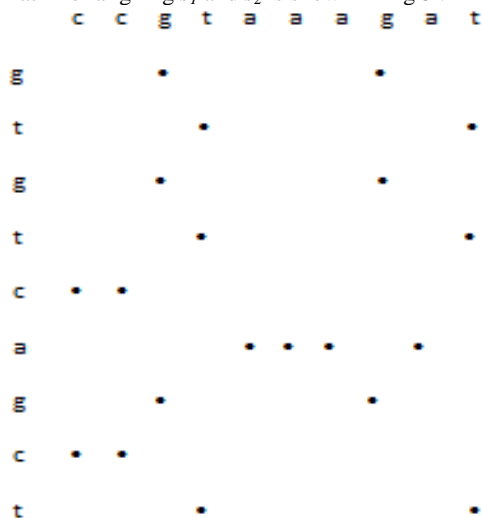


Fig 5: Dot matrix of sequences $s_1 = \text{ccgtaaagat}$ and $s_2 = \text{gtgtcaagctaactc}$.

The dots show all possible correspondences between the bases of the two sequences s_1 and s_2 , where each diagonal corresponds to a possible alignment. The best alignment happen when straight line of dots happen at the main diagonal of the dot plot matrix.

7. RESULTS AND DISCUSSIONS

7.1. Results Of Pairwise Alignment

First, we have made a code by using MATLAB program to make pairwise global alignment among the entire sequences of herpesviruses family.

7.1.1. The Results Obtained by Using Sequence Dot Plot Matrix

Fig 4 to Fig 10 represents the results of global pairwise alignment among the entire sequences of herpesvirus family by using sequence dot plot matrix. These figures are some of figures that obtained when making pairwise global alignment among each pair of viruses of herpesvirus family. We choose the figures that represent the highest similarity and this appear through the straight line of dots that represent the main diagonal in the dot plot matrix where it start from the left upper corner to the right lower corner as shown in figures. This straight line is an indicator for the degree of similarity between the two sequences as we mentioned before in the previous section.

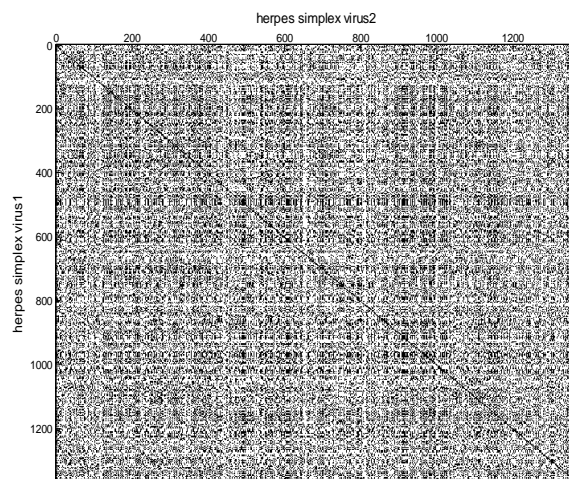


Fig 6: Sequence dot plot matrix between HSV1 and HSV2.

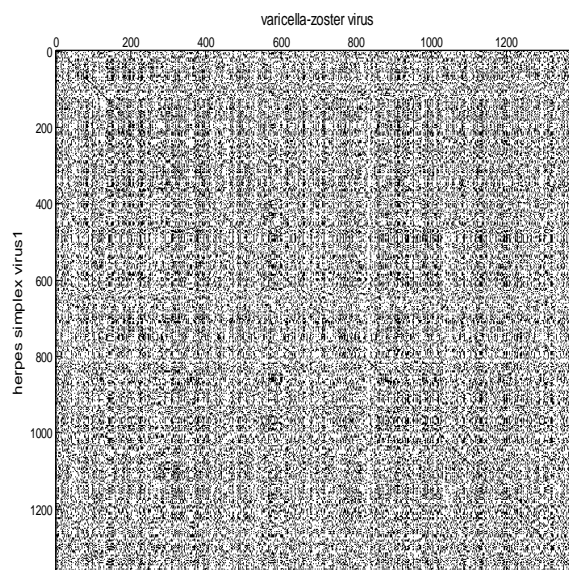


Fig 7: Sequence dot plot matrix between HSV1 and varicella-zoster virus.

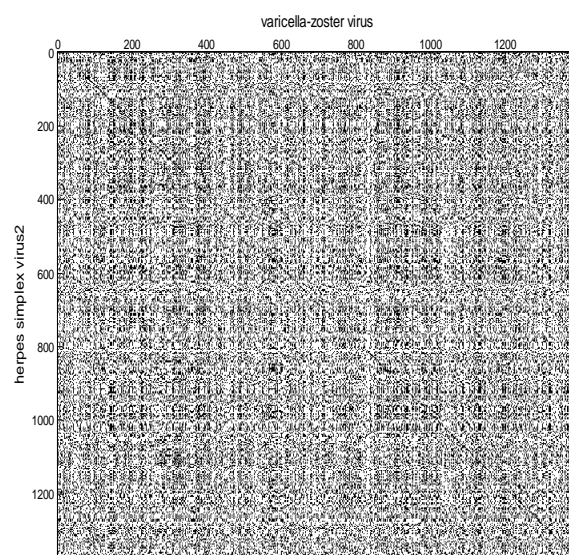


Fig 8: Sequence dot plot matrix between HSV2 and varicella-zoster virus.

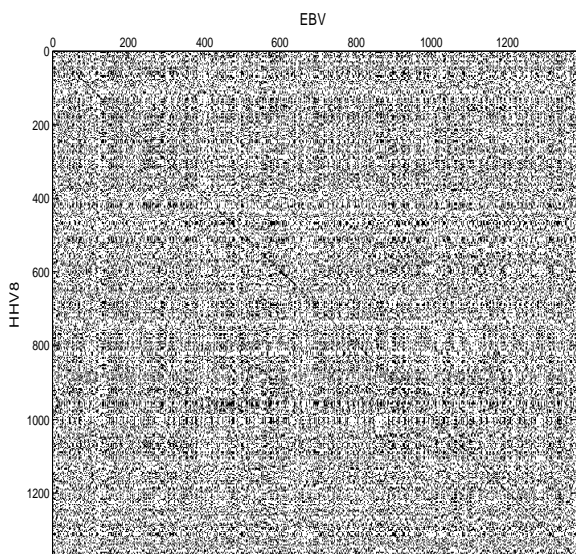


Fig 9: Sequence dot plot matrix between HHV8 and EBV.

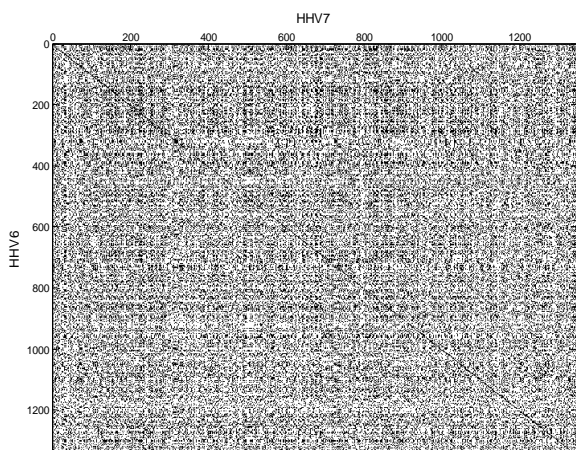


Fig 10: Sequence dot plot matrix between HHV6 and HHV7.

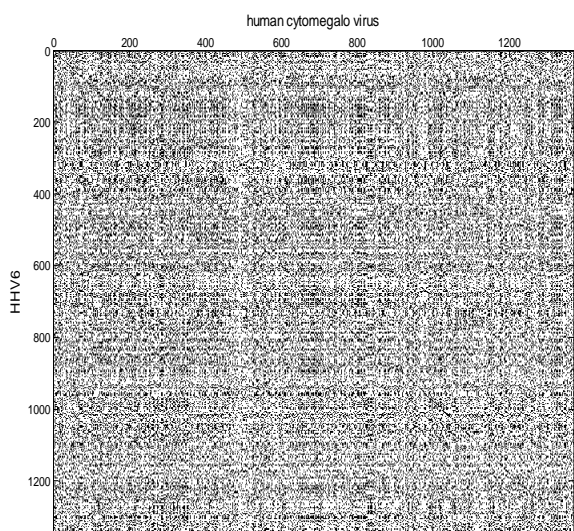


Fig 11: Sequence dot plot matrix between HHV6 and human cytomegalo virus.

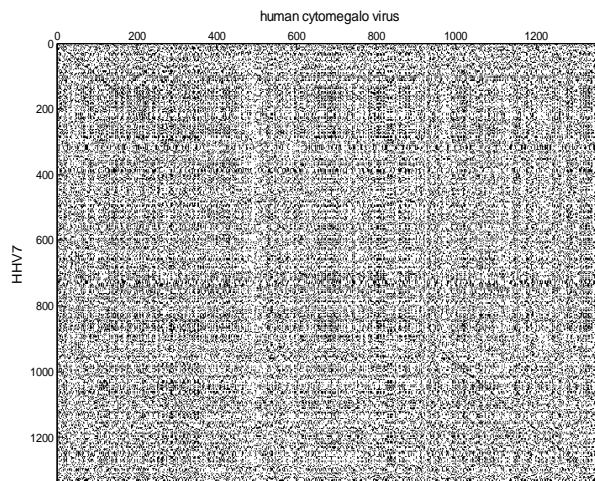


Fig 12: Sequence dot plot matrix between HHV7 and human cytomegalo virus.

7.1.2. The Results Obtained by Using Needleman-Wunsch Algorithm

In our study, we have used the following scoring matrices:-

- 1-Blosum50
- 2-Blosum30

The results were as in the following table:-

Table2: This table shows the score and the percentage of similarity (Identities) of the pairwise global alignment among the entire sequences of capsid protein of herpesvirus family.

Herpesviruse Family	Score by using Blosum50	Identities	Score by using Blosum 30	Identities
HSV1& HSV2	2940.33	94%	1848.8	94%
HSV1 & EBV	537.333	29%	423.2	28%
HSV1 & HHV6	503	26%	392	26%
HSV1 & HHV7	480	25%	373	25%
HSV1& HHV8	573.667	31%	438.8	30%
HSV1& Varicella-Zoster Virus	1641.67	52%	1061.4	52%
HSV1& Human Cytomegalo Virus	468.667	28%	375.4	27%
EBV & HSV2	541.667	28%	431.4	28%
EBV& HHV6	747.667	31%	533.8	31%
EBV& HHV7	726.667	32%	517.4	31%
EBV& HHV8	1780	56%	1128.6	56%
EBV & Varicella-Zoster Virus	551.667	28%	412.8	27%
EBV & Human Cytomegalo Virus	722.667	30%	507.8	30%
HSV2 & HHV6	493.667	26%	392.2	26%

HSV2 & HHV7	472	24%	372.8	25%
HSV2& HHV8	568	30%	436.6	30%
HSV2 & Varicella-Zoster Virus	1635	52%	1060	52%
HSV2& Human Cytomegalo Virus	470.333	27%	377	27%
HHV6 & HHV7	2182.67	68%	1371.4	68%
HHV6& HHV8	707	30%	500.2	30%
HHV6& Varicella-Zoster Virus	466.667	26%	371.4	26%
HHV6 & Human Cytomegalo Virus	1400.33	44%	899.8	44%
HHV7 & HHV8	710.667	31%	498	31%
HHV7 & Varicella-Zoster Virus	458	27%	359	26%
HHV7 & Human Cytomegalo Virus	1395.33	43%	893	44%
HHV8 & Varicella-Zoster Virus	555	29%	412.4	29%
HHV8 & Human Cytomegalo Virus	711.333	30%	506	30%
Varicella-Zoster Virus & Human Cytomegalo Virus	432.667	26%	347.2	26%

The results obtained in table 2 and figures from Fig 6 to Fig 12 conclude that:-

1. Capsid protein of herpes simplex1 is more similar to capsid protein of herpes simplex2 and also capsid protein of varicella-zoster virus.
2. Capsid protein of herpes simplex2 is more similar to capsid protein of varicella-zoster virus.
3. Capsid protein of Epstein barr virus is more similar to capsid protein of human herpes virus8.
4. Capsid protein of human herpes virus6 is more similar to capsid protein of human herpes virus7 and also capsid protein of human cytomegalo virus.
5. Capsid protein of human cytomegalo virus is more similar to capsid protein of human herpes virus7.

7.2. Results Of Multiple Sequence Alignment

Second, we have made a code by using MATLAB program to create multiple sequence alignment (MSA) among all the entire sequences of the capsid protein sequence. Multiple sequence alignment (MSA) is used to ensure and specify the results obtained in Table 1. The results are illustrated by using phylogenetic tree.

In our study, we have used the following scoring matrices:-

- 1- Blosum60
- 2- Blosum30
- 3- PAM10

7.2.1. Result obtain by using the scoring matrix BLOSUM60

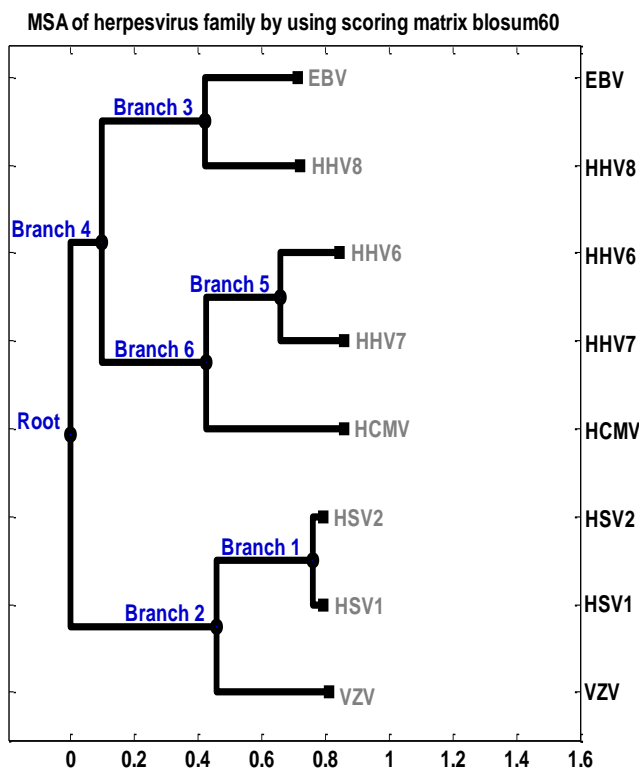


Fig 13: Results of MSA among the entire sequences of herpesvirus family by using the scoring matrix BLOSUM60

7.2.2. Result obtain by using the scoring matrix BLOSUM30

The result obtained when using scoring matrix BLOSUM30 is typical to that of BLOSUM60.

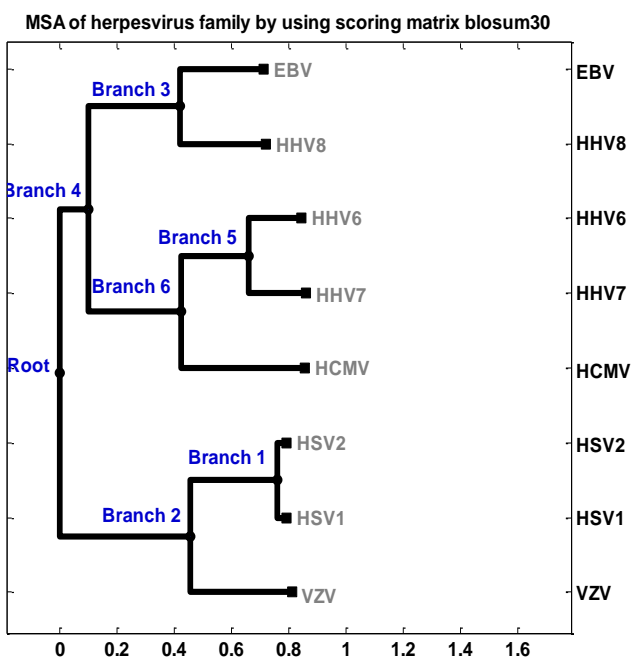


Fig 14: Results of MSA among the entire sequences of herpesvirus family by using the scoring matrix BLOSUM30.

7.2.3. Result obtain by using the scoring matrix PAM10

The result obtained when using scoring matrix PAM10 is typical to that of BLOSUM60 and BLOSUM30.

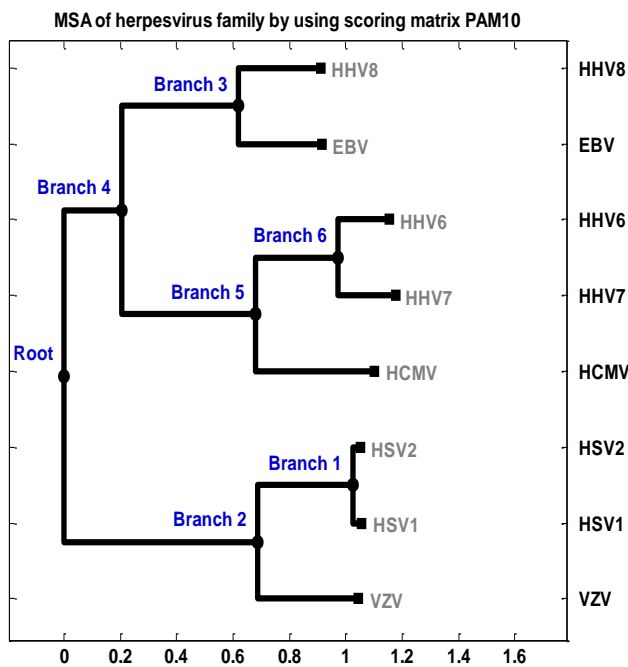
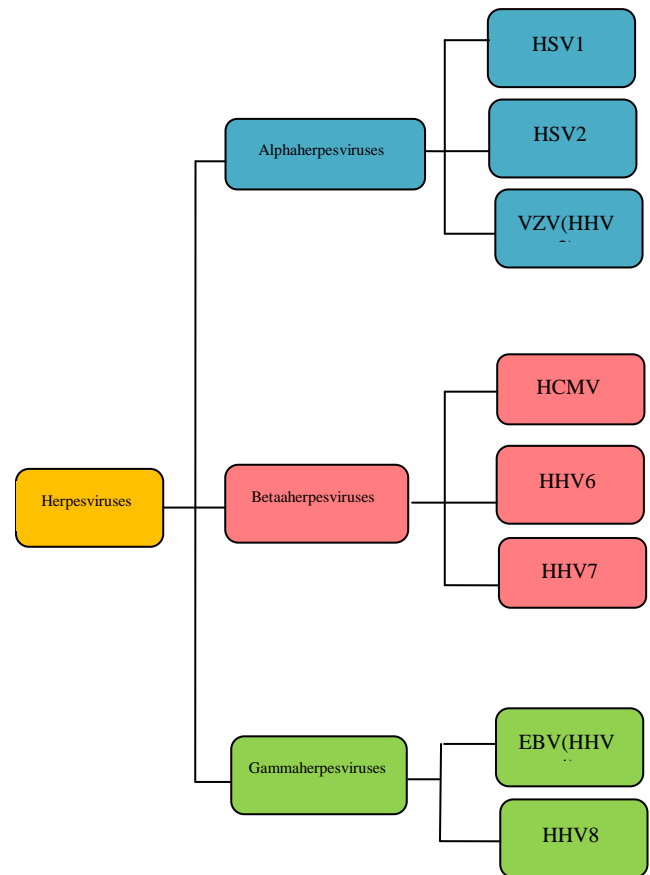


Fig 15: Results of MSA among the entire sequences of herpesvirus family by using the scoring matrix PAM10.



8. CONCLUSION

From the previous results obtained in figures from Fig 6 to 15 and Table 1 we can classify the herpesvirus family according to the similarity of the structure of their capsid protein into three categories as follows:-

1. The first category contain
 - a) Herpes simplex virus1 (HSV1)
 - b) Herpes simplex virus2 (HSV2)
 - c) Varicella-zoster virus VZV (HHV3)
2. The second category contain
 - a) Human herpesvirus7 (HHV7)
 - b) Human herpesvirus8 (HHV6)
 - c) Human cytomegalo virus HCMV (HHV5)
3. The third category contain
 - a) Human herpesvirus8 (HHV8)
 - b) Epstein barr virus (EBV)

The differences in capsid gene activation and expression need to be studied in depth by analysis its promoter region [25]. In addition, the structure similarity and evolutionary relationship between those viruses family and Genomic Retrotransposon based on structure [26, 27] and activation [28, 29, 30, 31] is currently under investigation.

9. ACKNOWLEDGMENTS

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