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22BIO201: Intelligence of Biological Systems - 1

Chaos Game Representation of DNA Sequences

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Contents

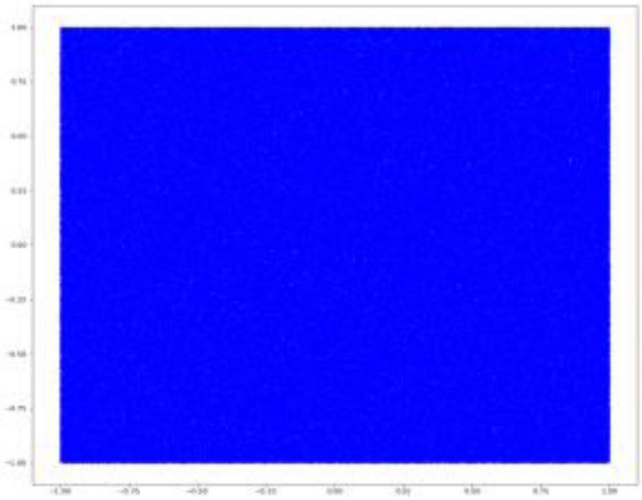
- CGR for sequence comparison
- CGR for COVID-19
- Frequency Chaos Game Representation(FCGR)
- FCGR probability matrix
- CGR Centroid method
- FCGR Probability Matrix distance
- CGR Centroid distance
- Hierarchical Agglomerative Clustering (HAC) analysis.

CGR for sequence comparison

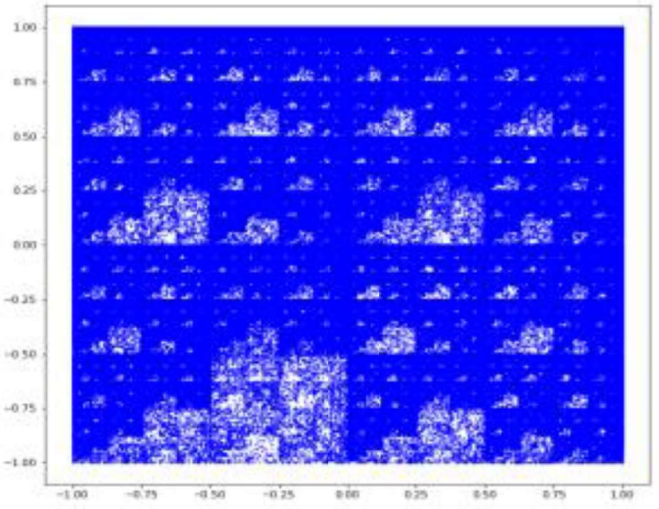
- Different and unique patterns in the CGR emerge from different sequences.
- CGR patterns of DNA segments have been proposed as a method for the classification and Identification of genomic sequences.
- CGR of DNA sequences coming from various species show pattern such as squares, parallel lines, rectangles, triangles, and also complex fractal patterns.
- Random sequence of DNA will not generate such a pattern
- CGR of same species (eg., virus genomes) look very similar visually.

CGR for sequence comparison

- While CGR can create fractals, it is not guaranteed to occur with every organism.
- Patterns differ between organisms as well
- Patterns formed by the CGR of prokaryotes differs from that of eukaryotes due to less variation in DNA



(a) Random Sequence CGR



(b) Human Chromosome 21 CGR

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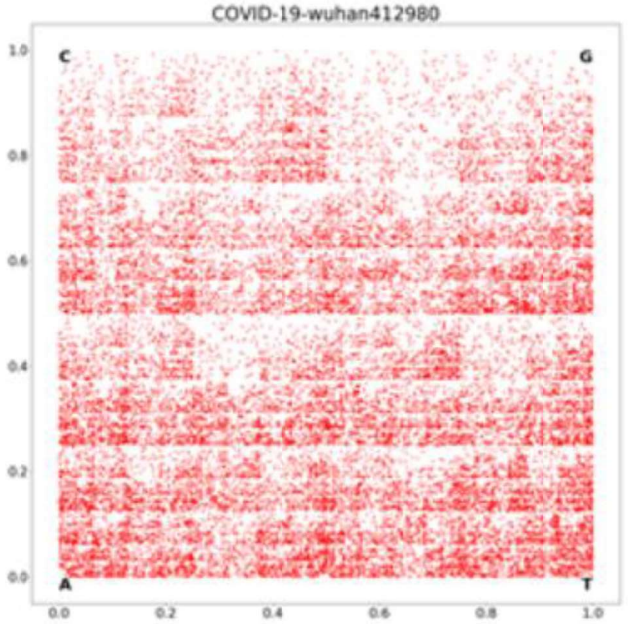
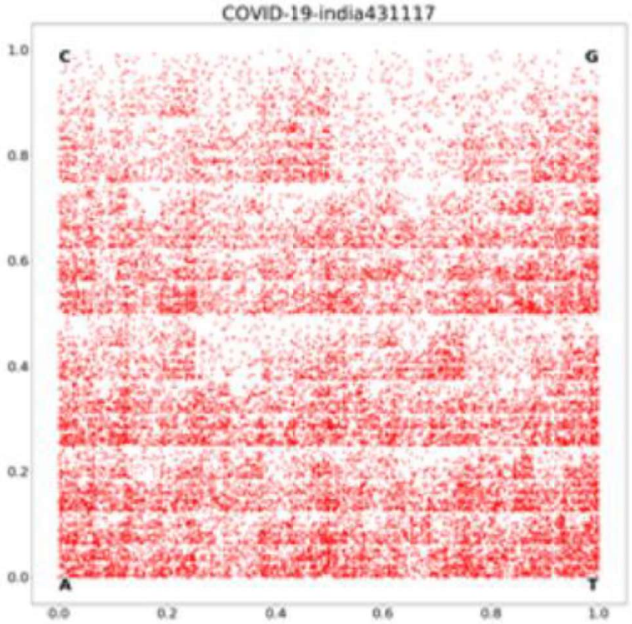
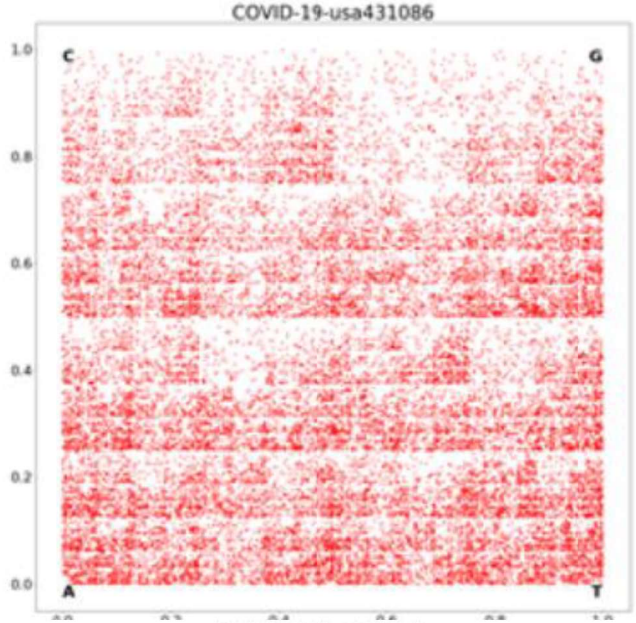
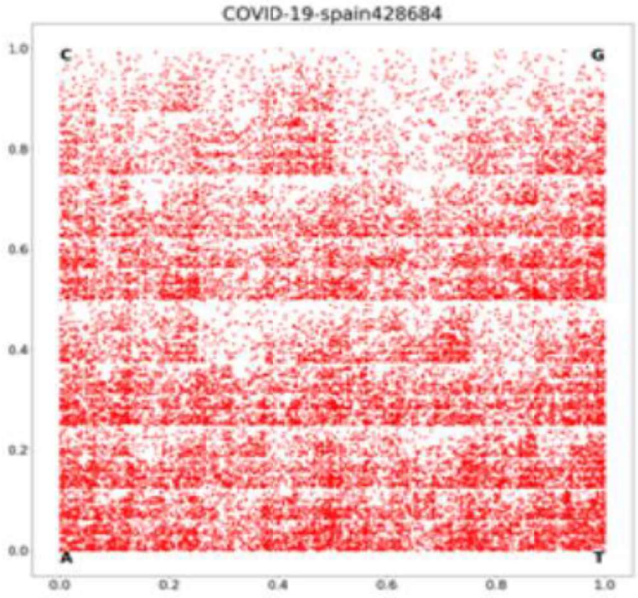
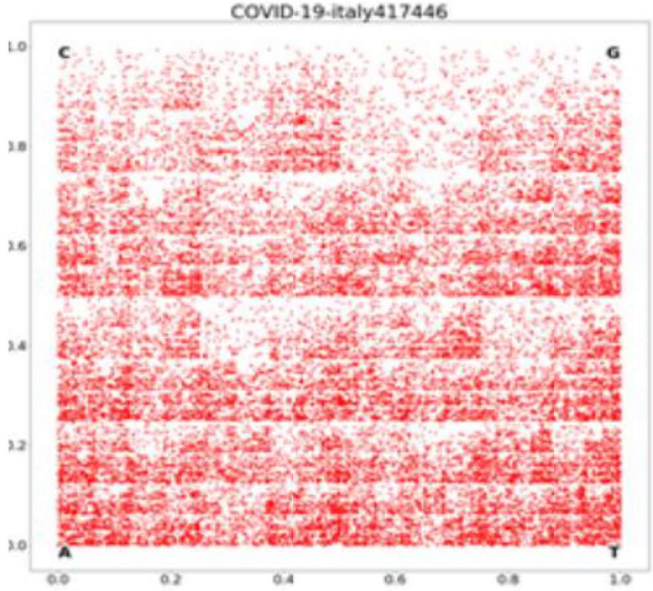
CGR for COVID-19

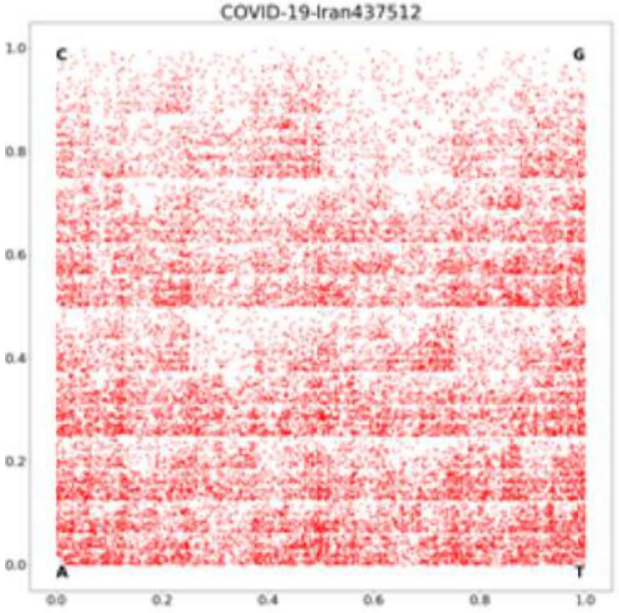












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CGR for sequence comparison

- Step1: Create CGR of Sequences
- Step2: Compute the FCGR Probability Matrix
- Step3: Calculate the centroid of each grid
- Step4: Measure the distance between two CGR images
  - FCGR Probability Matrix distance
  - CGR Centroid distance
- Step5: Create the dendrogram of the distance matrices using Hierarchical Agglomerative Clustering (HAC) analysis.

Frequency Chaos Game Representation(FCGR)

- A k-th order FCGR is a $2^k \times 2^k$ matrix that can be constructed by dividing the CGR plot into a $2^k \times 2^k$ grid, and defining the element |aij| as the number of points that are situated in the corresponding grid square.

First-order FCGR

$$FCGR_1(s) = \begin{pmatrix} N_C & N_G \\ N_A & N_T \end{pmatrix}$$

Second-order FCGR

$$FCGR_2(s) = \begin{pmatrix} N_{CC} & N_{GC} & N_{CG} & N_{GG} \\ N_{AC} & N_{TC} & N_{AG} & N_{TG} \\ N_{CA} & N_{GA} & N_{CT} & N_{GT} \\ N_{AA} & N_{TA} & N_{AT} & N_{TT} \end{pmatrix}.$$

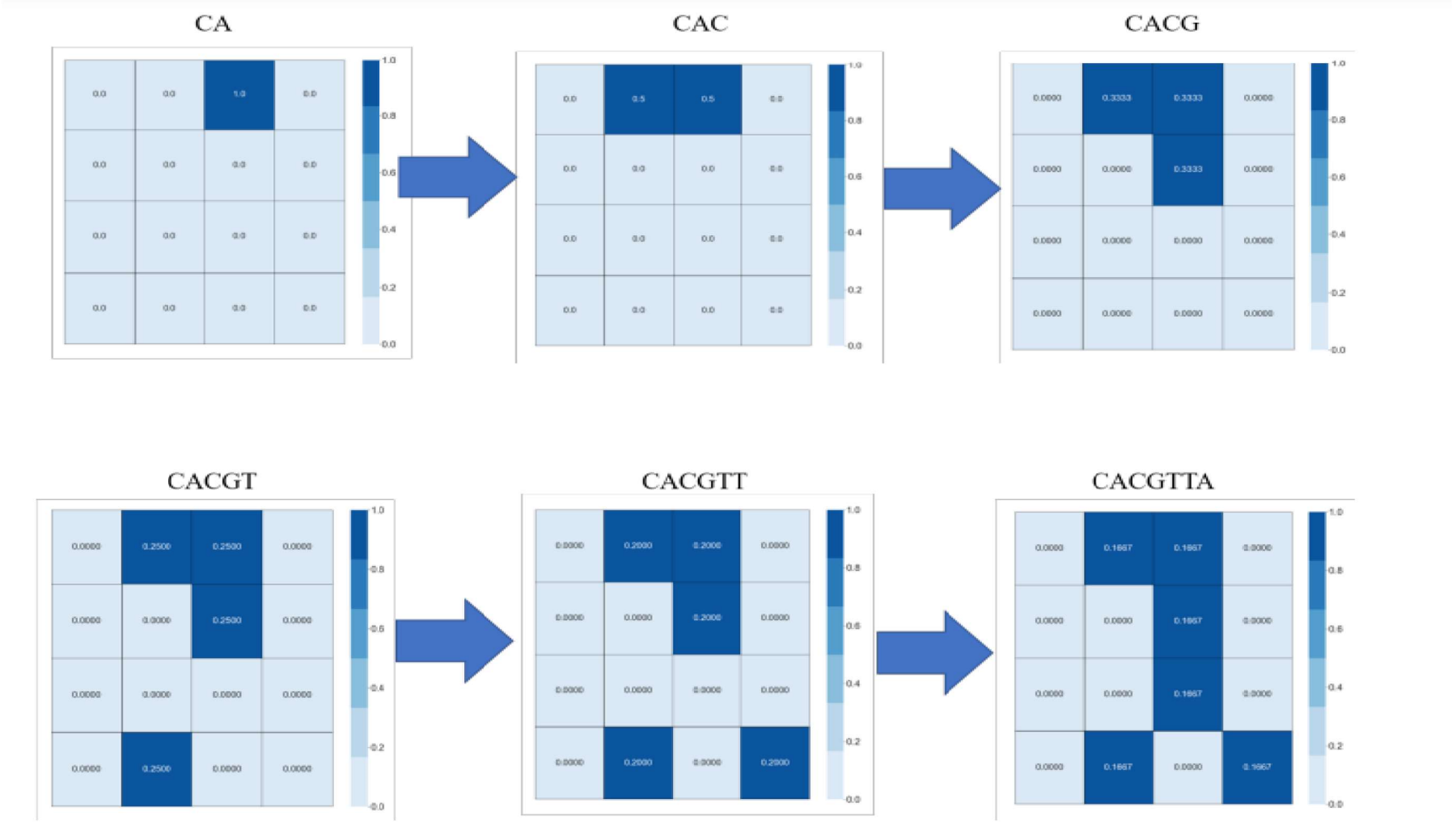
- $(k+1)^{th}$ order $FCGR_{k+1}(s)$ can be obtained by replacing each element N_X in $FCGR_k(s)$ with four elements $\begin{pmatrix} N_{CX} & N_{GX} \\ N_{AX} & N_{TX} \end{pmatrix}$ where X is a sequence of length k over the alphabet {A, C, G, T}

FCGR probability matrix

- If the generated square image has a size of $2^k \times 2^k$ pixels, then every pixel represents a distinct k-mer.
- For each $k \geq 1$, define a probability matrix of $FCGR_k(s)$ by taking each entry of $FCGR_k(s)$ dividing by the total counts of all k-mers.
- Probability matrix can be interpreted as probability of distribution.

$$(P_{ij}), 1 \leq i, j \leq 2^k. \qquad \sum_{i,j} P_{ij} = 1$$

FCGR probability matrix



An example of FCGR representation of the sequence CACGTTA

CGR Centroid method

- Centroid of a cluster of points is the mean of those points
- Let (x_k,y_k) be the coordinates of a point in the CGR. We define the centroid in each of the $2^k \times 2^k$ grid as follows:

$$C_{ij} = \left(\frac{\sum_{k=1}^{n} x_k}{n}, \frac{\sum_{k=1}^{n} y_k}{n} \right)$$

$$1 \leq i,j \leq 2^k$$

centroid is then calculated for each grid

FCGR Probability Matrix distance

- For two FCGR probability matrices (p_{ij}) and (p'_{ij}) , The distance between the two probability matrices

$$D_{PM} = \sum_{i=1}^{2^k} \sum_{j=1}^{2^k} d_{ij}.$$

where

$$d_{ij} = \left| p_{ij} - p'_{ij} \right|.$$

CGR Centroid distance

- For two centroids $c_{ij}=(x_{ij},y_{ij})$ and $c'_{ij}=(x'_{ij},y'_{ij})$ respectively for $1 \le i,j \le 2^k$, the centroid distance is

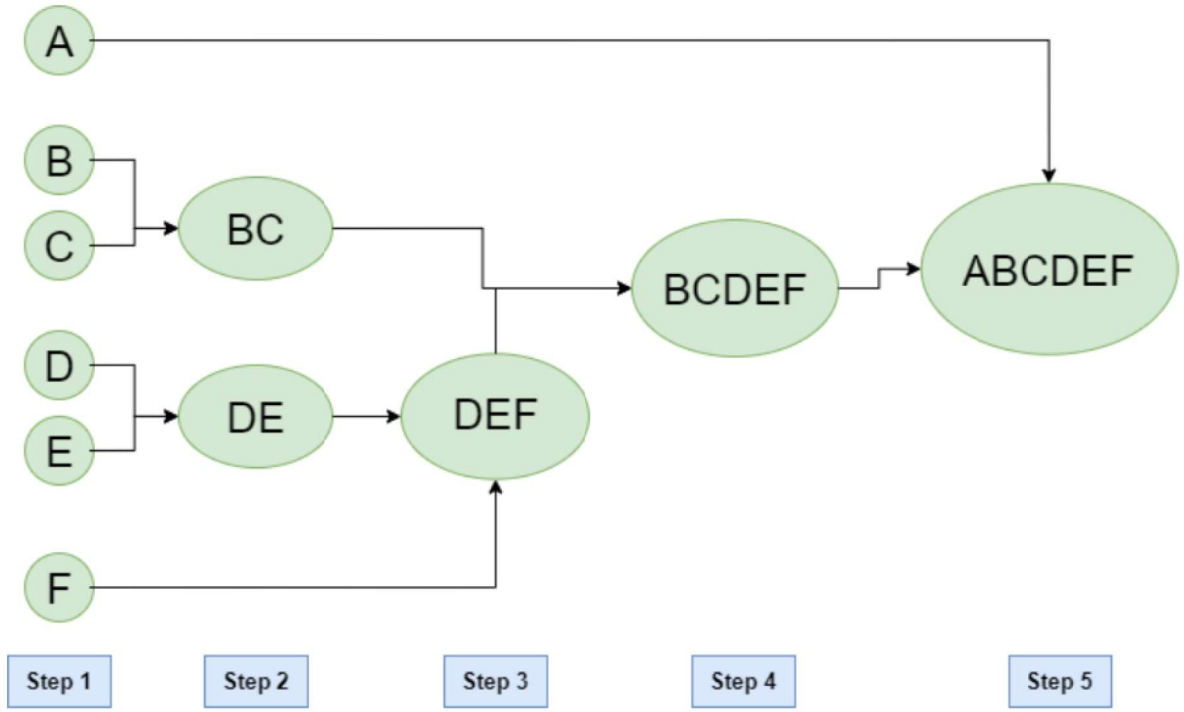
$$D_{cd} = \sum_{i=1}^{2^k} \sum_{j=1}^{2^k} d_{ij}.$$

where

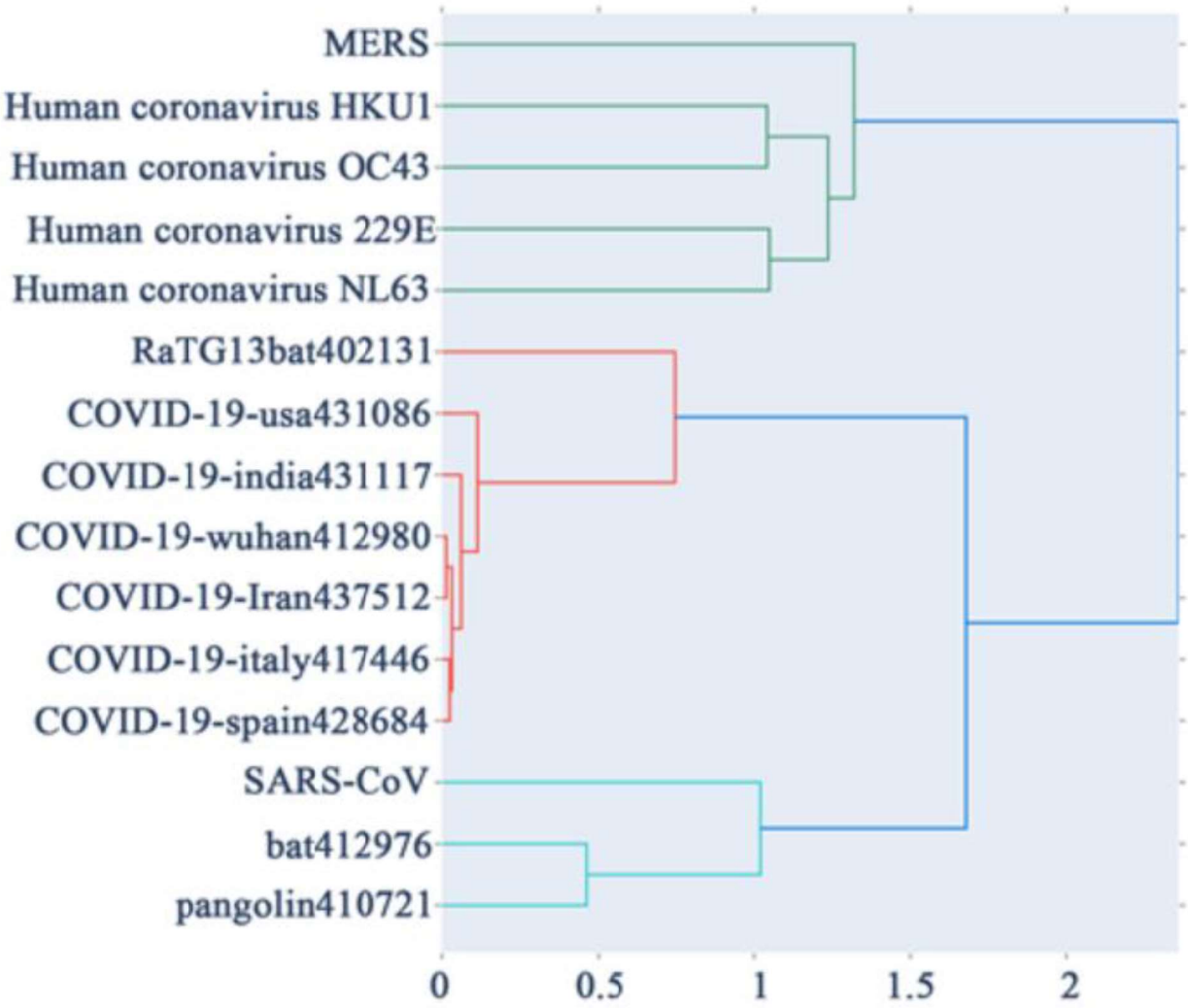
$$d_{ij} = \sqrt{(x_{ij} - x'_{ij})^2 + (y_{ij} - y'_{ij})^2}.$$

Hierarchical Agglomerative Clustering

- This clustering algorithm does not require us to prespecify the number of clusters.
- This Bottom-up algorithms treat each data as a singleton cluster at the outset and then successively agglomerate pairs of clusters until all clusters have been merged into a single cluster that contains all data.

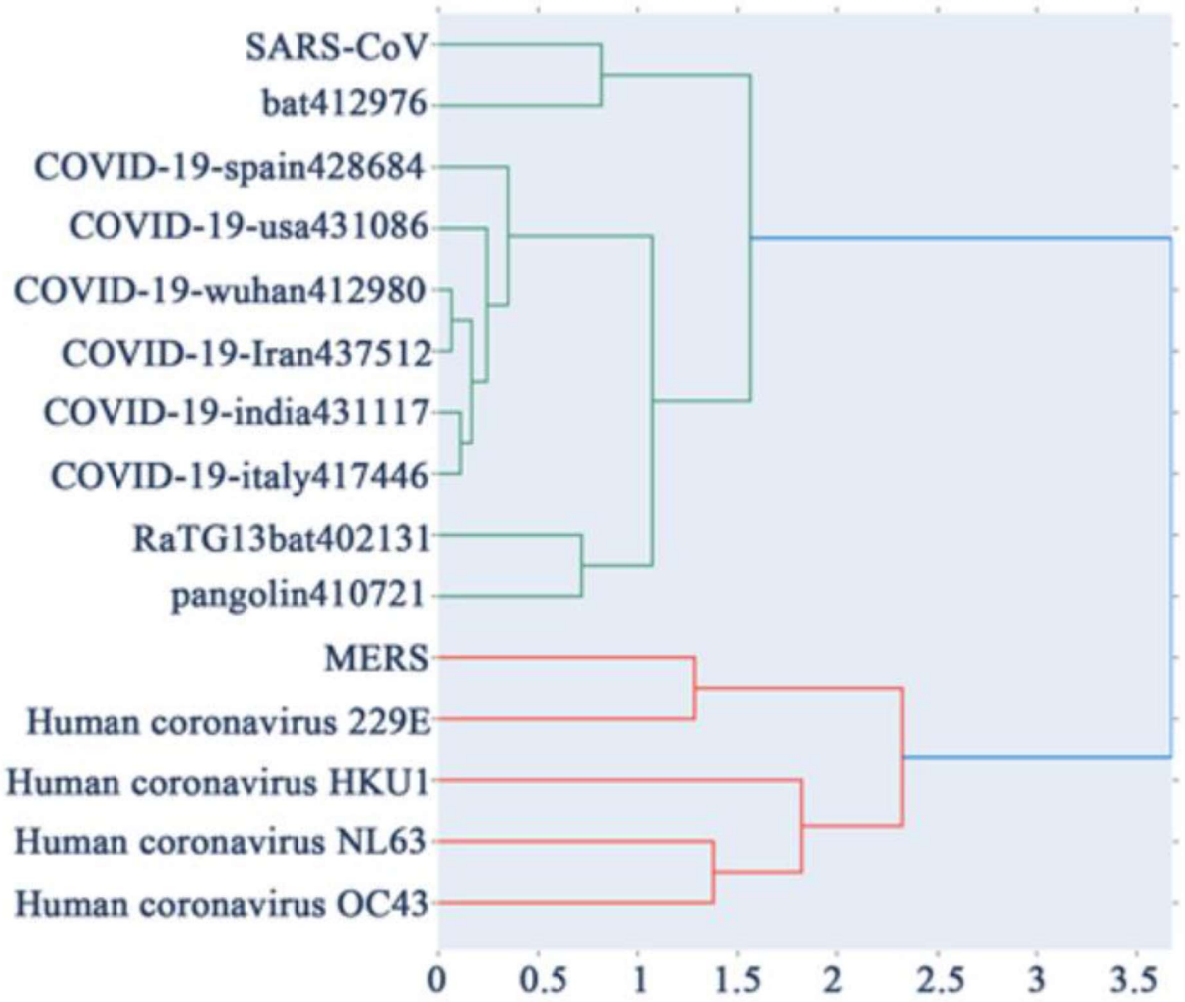


HAC Analysis



HAC phylogenetic tree using probability matrix distance.

HAC Analysis



HAC phylogenetic tree using CGR centroid distance

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