Input-Output Types of Fifteen Modules on Discrete and Real Measurements for COVID-19

Jeffrey Zheng (✉ conjugatelogic@yahoo.com)
Key Laboratory of Quantum Information of Yunnan, Key Laboratory of Software Engineering of Yunnan, Yunnan University
https://orcid.org/0000-0003-4225-7077

Minghan Zhu
Yunnan University

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Jeffrey Zheng, Minghan Zhu

Abstract Fifteen modules in the MAS provide unique functions to support wider applications. It is important to describe this set of transformation schemes from input genomes and output results using visualable numbers to briefly explain the transformation mechanism involved in each module. In this paper, vectors, matrices and various measurements are described following each module. From a genomic sequence, there are two types of outputs for three groups: 1) groups A & B related to discrete measurements represented in either vectors or matrices; 2) groups C related real measurements linked to entropy indices restricted in a limited line segment or a certain square region as a hierarchical organization. The main transformations and projections are described. Sample distributions and genomic index maps are illustrated.

Keywords: metagenomic analysis system, multiple modules, workflow, discrete measures, genomic index, geometric invariant

Jeffrey Zheng1,2
1 Key Laboratory of Quantum Information of Yunnan
2 Key Laboratory of Software Engineering of Yunnan
Yunnan University, Kunming, e-mail: conjugatelogic@yahoo.com

Minghan Zhu
Yunnan University e-mail: crystalj000@163.com

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Introduction

It is essential for readers to understand the basic functions of transforming modules in the metagenomic analysis system (MAS). Fifteen modules of three projections on the \{A,B,C\} groups in the MAS provide unique capacities to support wider applications. It is important to describe this set of transformation schemes from input genomes and output results relevant to vector or matrix using visual workflows to briefly explain the transformation mechanism involved in each module based on combinatorial algorithms, matrix theory, geometric measure theory, combinatorial topology, combinatorial enumeration, computational mathematics and advanced computational applications [1]-[19].

In this paper, vectors, matrices and various measurements are described relevant to wider applications on variant construction [35]-[42] following each module as a complementary supporting documentation for the first paper “A Visual Framework of Meta Genomic Analysis on Variations of Whole SARS-CoV-2 Sequences” in this special issue.

From a genomic sequence, there are two types of outputs for three groups: 1) the A & B groups related to discrete measurements represented in either vectors or matrices; 2) the C groups related real measurements linked to entropy indices restricted in a limited line segment or a certain square region as a hierarchical organization. The main transformations and projections are described. Sample distributions and genomic index maps are illustrated.

Materials and Methods

Input on Four Meta Symbols

Since the MAS is focused on genomes, each element of input sequences is composed of four meta symbols: \{A,C,G,T\} mapping to the four numbers \{0,1,2,3\} in 1-1 correspondences.

The First and Second Orders of Combinations

From a combinatorial viewpoint, the first-order combination from the four symbols is composed of sixteen states as a lattice of hierarchy, as shown in Fig. 1(a).

The sixteen states \{\emptyset, A, C, G, T, \cdots, ACGT\} can be mapped into the sixteen numbers \{0, 1, 2, \cdots, 15\} to represent a 1D linear structure with 16 distinct positions.

The second-order combinations are composed of 2D $16 \times 16$ pairs of states or a 2D square with 256 positions.
Multiple Probability Measures

When a genome contains $m$ elements, the numbers of four meta symbols can be counted. Let $m_s, s \in \{A, C, G, T\}$ be a number of symbols $s$ and $p_s$ be a probability measure. We have the following equations for the multiple probability measures.

\[
m = m_A + m_C + m_G + m_T
\]
\[
p_s = \frac{m_s}{m}, s \in \{A, C, G, T\}
\]
\[
1 = p_A + p_C + p_G + p_T
\]

Conditional Probability Measures

For the conditional probability measures shown in Fig. 1(b), let $\tilde{p}_s$ be a conditional probability measure on $s$, and the following equations are satisfied.

\[
p_0 = \frac{m_C + m_T}{m} = p_C + p_T
\]
\[
p_1 = \frac{m_A + m_G}{m} = p_A + p_G
\]
\[
1 = p_0 + p_1
\]
\[
\tilde{p}_C = \frac{m_C}{m_C + m_G}
\]
\[
\tilde{p}_G = \frac{m_G}{m_C + m_G}
\]
\[ \tilde{p}_A = \frac{m_A}{m_A + m_T} \]
\[ \tilde{p}_T = \frac{m_T}{m_A + m_T} \]
\[ 2 = \tilde{p}_A + \tilde{p}_C + \tilde{p}_G + \tilde{p}_T \]

Under multiple and conditional probability conditions, there are ten distinct probability measures \( \{p_0, p_1, p_A, p_C, p_G, p_T, \tilde{p}_A, \tilde{p}_C, \tilde{p}_G, \tilde{p}_T\} \).

**Three Workflows from Input to Output**

Three workflows can be identified by the type of output.

1. Input: Vector → Processes in Group A → Output: Vector
2. Input: Vector → Processes in Groups A/B → Output: Matrix
3. Input: Vector → Processes in Group C → Output: Real Numbers

**Three Output Types**

There are three distinct types of output for fifteen modules that correspond to vector, matrix and real number.

In the most three projections of the \( \{A, B, C\} \) groups, both vector and matrix can be distinguished from their basic elements into three categories: genomic (four values), integer (multiple values), probability (rational values) and similarity measures (real values) to represent genomic sequences, counting, probability and similarity measures, respectively.

In the last workflows of the C groups, it uses real numbers to represent various entropy parameters as the output values.

**Nine Modules in Global Projection**

Nine modules \( \{1DS, 2DS, RDG, PC, 1DL, MD, WP, KP, 3DV\} \) are described in three parts as input, output and process.

\( A_1: \) 1DS similarity comparison between two sequences in m-mers.

\[
\begin{align*}
\text{Input} & : N \text{ (a genome vector with } N \text{ elements)} \\
\text{Output} & : M \text{ (a similarity vector with } M \text{ elements)} \\
\text{Process} & : N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} M \xrightarrow{\text{Vector}} M \\
\text{CF} & : 16 \text{(total number of selections)}
\end{align*}
\]
A2: 2DS similarity comparison on one sequence in M segments.

\[
\begin{align*}
\text{Input: } & N \\
\text{Output: } & M \times M \text{ (a similarity matrix with } M \times M \text{ elements)} \\
\text{Process: } & N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} M \xrightarrow{\text{Matrix}} M \times M \\
\text{CF: } & 32 \text{ (total number of selections)}
\end{align*}
\]

A3: MCP multiple and conditional probability measures of m elements in a segment.

\[
\begin{align*}
\text{Input: } & N \\
\text{Output: } & m + 1 \text{ (a probability vector with } m + 1 \text{ elements)} \\
\text{Process: } & N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m + 1 \xrightarrow{\text{Vector}} m + 1 \\
\text{CF: } & 10 \text{ (total number of selections)}
\end{align*}
\]

A4: PC protein coding of m elements in a segment.

\[
\begin{align*}
\text{Input: } & N \\
\text{Output: } & M \text{ (a protein coding vector with } M \text{ elements)} \\
\text{Process: } & N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} M \xrightarrow{\text{Vector}} M \\
\text{CF: } & 16 \text{ (total number of selections)}
\end{align*}
\]

A5: 1DL 2D to 1D linearized transformation for m elements in a segment.

\[
\begin{align*}
\text{Input: } & N \\
\text{Output: } & (m + 1)^2 \text{ (a linearized probability vector with } (m + 1)^2 \text{ elements)} \\
\text{Process: } & N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m + 1 \xrightarrow{\text{Matrix}} (m + 1) \times (m + 1) \xrightarrow{\text{Vector}} (m + 1)^2 \\
\text{CF: } & 256 \text{ (total number of selections)}
\end{align*}
\]

A6: MD momentum distributions of probability measurements of m elements in a segment.

\[
\begin{align*}
\text{Input: } & N \\
\text{Output: } & M \text{ (a momentum probability vector with } M \text{ elements)} \\
\text{Process: } & N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} M \xrightarrow{\text{Vector}} M \\
\text{CF: } & 16 \text{ (total number of selections)}
\end{align*}
\]

A7: WP whole/parts in n partitions.

\[
\begin{align*}
\text{Input: } & N, n
\end{align*}
\]
Output: \((m+1) \times (m+1)\) (a projective matrix with \((m+1) \times (m+1)\) elements)

Process:

\[
N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m+1 \xrightarrow{\text{Matrix}} (m+1) \times (m+1)
\]

Combinatorial Matrix \((m+1) \times (m+1)\)

\[
CF: \quad 256 \times 2^n \text{ (total number of selections and combinations)}
\]

A\(_8\): KP K-mer process of \(m\) elements in a segment.

Input: \(N, 0 < m \leq T\)

Output: \((m+1) \times (m+1)\)

(a series of projective matrices with \((m+1) \times (m+1)\) elements)

Process:

\[
N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m+1 \xrightarrow{\text{Matrix}} (m+1) \times (m+1)
\]

\[
CF: \quad 256 \times T \text{ (total number of selections and combinations)}
\]

A\(_9\): 3DV transforming 2D map to 3D visualization of \(m\) elements in a segment.

Input: \(N\)

Output: \(f[(m+1) \times (m+1)]\) (a visual matrix with \((m+1) \times (m+1)\) elements)

Process:

\[
N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m+1 \xrightarrow{\text{Matrix}} (m+1) \times (m+1)
\]

Visual Matrix \(f[(m+1) \times (m+1)]\)

\[
CF: \quad 256 \text{ (total number of combinations)}
\]

Two Modules in Clustering Projection

Two modules \{IDM, CDM\} are described in three parts as input, output and process.

B\(_1\): IDM \(256 \times [(m+1) \times (m+1)]\) density matrix and integration.

Input: \(N\)

Output: \((256+1) \times [(m+1) \times (m+1)]\)

(257 matrices each with \((m+1) \times (m+1)\) elements)

Process:

\[
N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m+1 \xrightarrow{\text{Matrix}} (m+1) \times (m+1)
\]

Combinatorial 256 \(\times [(m+1) \times (m+1)]\)

Integration \(\rightarrow [(m+1) \times (m+1)]\)

\[
CF: \quad 1
\]

B\(_2\): CDM \(256 \times [(m+1) \times (m+1)]\) clustering density matrix and integration.

Input: \(N\)
Input-Output Types of Fifteen Modules

Output: \((256 + 1) \times [(m + 1) \times (m + 1)]\)
(a selection involved 257 matrices each with \((m + 1) \times (m + 1)\) elements)

Process: \(N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m + 1 \xrightarrow{\text{Matrix}} (m + 1) \times (m + 1)\)
Selection \(256 \times [(m + 1) \times (m + 1)]\)
Integration \( [(m + 1) \times (m + 1)]\)

\(CF: 2^{(m+1)²}\) (total number of selections)

Four Modules in Genomic Index Projection

Four modules \(\{CE, IE, ME, TE\}\) are described in three parts as input, output and process.

\(C_1: CE\) one of 16 combinatorial entropies.

\(Input: N\)
\(Output: 1\) (a real number \(\in [0, \log_2(m + 1)]\))

Process: \(N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m + 1 \xrightarrow{\text{Combination}} 16 \times (m + 1)\)
Entropy \(\rightarrow 16\) Selection \(\rightarrow 1\)

\(CF: 16\) (total number of selections)

\(C_2: IE\) an integrated entropy.

\(Input: N\)
\(Output: 1\) (a real number \(\in [0, \log_2(m + 1)]\))

Process: \(N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m + 1 \xrightarrow{\text{Combination}} 16 \times (m + 1)\)
Integration \(\rightarrow (m + 1)\) Entropy \(\rightarrow 1\)

\(CF: 1\)

\(C_3: ME\) a mean entropy.

\(Input: N\)
\(Output: 1\) (a real number \(\in [0, \log_2(m + 1)]\))

Process: \(N \xrightarrow{\text{Segment}} m \times M \xrightarrow{\text{Measure}} m + 1 \xrightarrow{\text{Combination}} 16 \times (m + 1)\)
Entropy \(\rightarrow 16\) Mean \(\rightarrow 1\)

\(CF: 1\)

\(C_4: TE\) a topological entropy[32].
**Input:** N

**Output:** 1 (a real number \( \in [0, 1] \))

**Process:** \( N \xrightarrow{m-mer Segment} m \times N \xrightarrow{Counting} \leq N \xrightarrow{T-Entropy} 1 \)

**CF:** 1

### Entropy Measurements

Different from various probability measures in three projections, entropy measurements based on thermodynamics, thermostatistics, statistics and statistical mechanics [20]-[34] are calculated from all \( M \) segments to collect relevant information on distributions on \((m+1)\) vectors or \((m+1)^2\) matrices. The possible schemes are \{A3, A5, A7, A8, A9, B1, B2\} modules to evaluate their entropy properties. For the other four modules \{A1, A2, A4, A6\}, all outputs are linked to \( M \) segments. It is essential to apply statistical operations to arrange intermediate outputs to satisfy the format under either \( m+1 \) or \((m+1)^2\) conditions, and then their entropy measurements can be evaluated further.

Let a vector \( Z \) with \((m+1)\) elements, \( Z = (Z_0, Z_1, \ldots, Z_j, \ldots, Z_m) \), \( 0 \leq Z_j \leq M \) and \( M = \sum_{j=0}^{m} Z_j \). Under this condition, let \( P_j = \frac{Z_j}{M} \) be the \( j \)-th probability measurement, and a relevant information entropy \( ZE \) can be determined and restricted in a \([0, \log_2(m+1)]\) region.

\[
ZE = - \sum_{j=0}^{m} P_j \log_2(P_j), \quad ZE \in \mathbb{R}
\]

\[
1 = \sum_{j=0}^{m} P_j, \quad 0 \leq j \leq m
\]

\[
\forall ZE \in [0, \log_2(m+1)]
\]

Let a matrix \( Z' \) with \((m+1)^2\) elements, \( Z' = (Z'_0, Z'_1, \ldots, Z'_j, \ldots, Z'_{(m+1)^2-1}) \), \( 0 \leq Z'_j \leq M \) and \( M = \sum_{j=0}^{(m+1)^2-1} Z'_j \). Under this condition, let \( P'_j = \frac{Z'_j}{M} \) be the \( j \)-th probability measurement, and a relevant information entropy \( Z'E \) can be determined and restricted in a \([0, 2 \times \log_2(m+1)]\) region.

\[
Z'E = - \sum_{j=0}^{(m+1)^2-1} P'_j \log_2(P'_j), \quad Z'E \in \mathbb{R}
\]
\[
1 = \sum_{j=0}^{(m+1)^2-1} P'_j, \quad 0 \leq j < (m+1)^2 \\
\forall Z' E \in [0, 2 \times \log_2(m+1)]
\]

**Topological Entropy**

Different from the other three entropies, topological entropy [32] is based on another set of equations. Let \( P_Z(m) \) be the number of different \( m \)-length subwords (overlaps allowed) that appear in \( Z \). Topological entropy \( ZE \) satisfies the following equation.

\[
ZE = \lim_{m \to \infty} \frac{\log_4 P_Z(m)}{m}, 0 \leq ZE \leq 1
\]

Under this formula, a genome \( Z \) is composed of a set of subwords \( P_Z(m) \) to be transformed into a topological entropy restricted in the \([0,1]\) region.

Applying multiple entropy measurements, it is feasible to extend multi-tuples of regions to be square (two values), cube (three values) and so on to distinguish refined projections into higher dimensional geometries in detail.

**Table 1** Input and output types of fifteen modules in the \{A, B, C\} projections

| Module | Input (Vector) | Output Type | Description |
|--------|----------------|-------------|-------------|
| A1     | N, M           | vector real | 1D similarity measures |
| A2     | N, M           | matrix real | 2D similarity measures |
| A3     | N, \((m+1)\)   | vector rational | ten probability measures |
| A4     | N, M           | vector integer | 1D momentum probability |
| A5     | N, \((m+1)^2\) | vector integer | 2D to 1D linearized measures |
| A6     | N, M           | vector integer | 1D momentum probability |
| A7     | N, \((m+1)^2\) | matrix integer | 2D whole/parts in \( n \) portions |
| A8     | N, T           | matrix integer | K-mer hierarchy of measures |
| A9     | N, \((m+1)^2\) | matrix rational | 2D to 3D visualization |
| B1     | N, T           | \(257 \times [(m+1)^2]\) matrices rational | density matrices & Integration |
| B2     | N              | \(257 \times [(m+1)^2]\) matrices rational | clustering density mat. & integ. |
| C1     | N              | 1 scale real | combinatorial entropy |
| C2     | N              | 1 scale real | integrated entropy |
| C3     | N              | 1 scale real | mean entropy |
| C4     | N              | 1 scale real | topological entropy |
Results and Discussion

Sample Results

A list of sample results on various modules \{A1, A5, A9, B1, B2, C1, C2, C3, C4\} are selected for illustrations as follows.

A1: Various curves of (A+T)% measures in multiple segments
Input-Output Types of Fifteen Modules

A5: 2D to 1D linearized measures in visual maps

A9: 2D visual

A9: 3D visual

A9: 3D visual projection
B1: 257 maps on integrated density matrices

B2: 257 maps on clustering density matrices
C1: 381 SARS-CoV-2 genomes on 1D & 2D combinatorial genomic index maps
(C3,C2): 32 genomes on 2D (mean, integrated) genomic index maps

(C3,C2): 62 genomes on 2D (mean, integrated) genomic index maps

(C3,C2): 128 genomes on 2D (mean, integrated) genomic index maps
C4: 1337 SARS-CoV-2 genomes on 1D & 2D topological genomic index maps.
Discussion

Visual distributions of the A1 module represent multiple genomes under multiple segments to show $AT - GC$ and $AT\%$ measuring curves. Checking either USA or China genomic sequences, various similarities or different parts can be identified.

Visual distributions of the A5 module show SARS-CoV-2 genomes collected from G20 regions and their refined 2D to 1D linearized measures. Checking each distribution, similarities and differences of various groups can be recognized.

In the A9 module, three sets of samples are selected from 2D maps, and 3D visual and projections are illustrated. Different coronaviruses can be distinguished by their 3D distributions.

A total of 256 maps and one integrated map of the B1 module are shown. Two sets of 256 clustering maps and integrated maps of the B2 module are selected. They are significantly different patterns with reflection and 90 degree rotational symmetries on two integrated maps.

In addition to sample results in the \{A,B\} groups, further samples were selected from the C groups. Under the C1 module, 281 genomes were selected to be transformed by 2D combinatorial genomic indices. A 2D genomic index map is created. Genomes were collected from various regions in four countries: the USA, China, Australia, and Belgium. The first two rows are shown in two X-Y projections for the four countries for both horizontal and vertical projections in eight 1D histograms. The following three rows were contained in various regions that could be further separated in the relevant 1D histogram. Very rich distributions and projections could be observed.

Three sets of sample results were selected for the \{C2, C3\} modules composed of horizontal axis in the C2 mean genomic index and vertical axis in the integrated genomic index. Left maps with phase-shifting effects and right maps were after further mean operations were performed. Three sets of results were contained in the \{32, 62, 128\} genomes. Significant visual differences could be observed.

A total of 1337 genomes were collected and illustrated for the C4 modules. The first two rows were 1D topological genomic index maps for eight countries. The following three rows were 2D topological genomic index maps and separated results for five countries. It is interesting to see significant differences among various countries from genomic index maps with extremely different distributions from distinguished regional maps.

Conclusion

As a complementary document, this paper provides additional information to support the first paper “A Visual Framework of Meta Genomic Analysis on Variations of Whole SARS-CoV-2 Sequences” for any person who would like to understand functions of the MAS in general. From workflows of fifteen modules and their input-output data types, three types of data forms, vector, matrix and real number, are
identified for the MAS. The superpowerful capacities were built from a set of entropy parameters under thermodynamics, thermostatistics and statistical mechanics. Multiple genomic index maps were shown as examples to illustrate this invariant quantitative measurement with supersymmetric properties in wider projections to provide global identifications on complicated genomes on a restricted region with infinite small scaling capacities. Further theoretical explorations and practical applications are required to be deeply explored in future activities.

Conflict Interest

No conflict of interest has been claimed.

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Figures

Figure 1

Four symbols in hierarchies; (a) sixteen combinations of four meta symbols in the first order on a lattice; (b) conditional probability structure