Journal of Microbial Pathogenesis

Nwankwo et al, J Microb Path 2017, 1:1

Research Article Open Access

American Center for Calculation of Biological Functionalities: A Multidisciplinary Forum for Designing Therapeutic Interventions and Determining Disease Pathogenesis

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Received date: November 08, 2017; **Accepted date:** November 25, 2017; **Published date:** November 30, 2017

Abstract

Background: Bio-functionalities including disease characteristics are known to be associated with protein sequence alterations (mutations). As a result, determination of disease processes and progression (pathogenesis), and provision of biomedical devices through calculating and analysing these functionalities have become the most vital and rational procedure to understanding and managing them. Engaging computerized bioinformatics procedures such as the Digital Signal Processing (DSP)-based technique called Informational Spectrum Method (ISM) therefore remains a better approach. Using ISM, we have earlier demonstrated HIV/SIV pathogenesis, investigated their evolutionary roadmaps, predicted their tropism, designed biomedical devices and assessed resistance offered to several classes of drugs. More investigations are required in other areas like Cancer, Autism, etc. Additionally, more devices need be developed.

Aim: The aim of this submission is to recommend a computerized bioinformatics-based Center for calculating biological functionalities for purposes of multidisciplinary investigations, and designing of biomedical devices.

Methods: Recommended procedures for this Center for the Calculation of Bio-functionalities will include Digital Signal Processing (DSP)-based techniques such as Informational Spectrum Method (ISM), and Resonant Recognition Method (RRM).

Results: Preliminary investigations using the recommended procedures have been found to be fruitful. Over 1000 proteins of HIV, HSP, TNF, Plasmodium, Ebola, and others have been investigated using these procedures. This has resulted in the designing of drugs, vaccines, their candidates, free online tools and biomedical devices such as Computer-Aided Drug Resistance Calculator.

Discussions: To effectively carry out these investigations, which employ both vast deposits of sequence information and computerized bioinformatics-based techniques, teamwork hence a Center is required.

Conclusions: The Center is envisioned to provide multidisciplinary, rational, more accurate and quantifiable bio-assessments. Appropriate engagement of all sequences and Amino Acid Scales is required in order to obtain accurate results.

Keywords Bio-functionalities; Bioinformatics; Computerized; Digital Signal Processing; Informational Spectrum Method

Introduction

Under natural selection (disease process) or it artificial counterpart (drug and other environmental pressures, and others), proteins are known to evolve from their conserved sequence alignment status to sequence alterations (mutations). This is with the view of fine-tuning their functions, modifying their functional sites or interacting with other substances [1]. Mutations can be beneficial, and in such situations, new functionalities or fitness to the structure are obtained in order to foster the well-being of the protein, hence the entire system. Alternatively, mutations can be pathogenic (disease-causing). This may result in reduced functionalities such as drug resistance, increased defence against host immunity or defect in proteomic development that precipitate diseases like Sickle Cell Anaemia [1]. Mutations have also been identified to assist pathogenic microorganisms escape host defence [2]. It has therefore been recognized that at molecular level, disease characteristics have been linked to sequence-alterations (mutations) of the proteins involved.

Pathogenesis refers to disease mechanisms or developmental procedures [3]. It goes beyond life cycles of the pathogenic agents as there is a continuous struggle to maintain well-being after maturation. Viral pathogenesis has been described as the developmental processes by which viral infection translates into diseases [3]. Its mechanisms, which include implantation, replication and spread, are affected by viral accessibility and susceptibility. Viral accessibility and susceptibility are determined by conditions such as viral affinity to

specific body tissues that is governed by receptiveness of the pathogens to the host cells (Tropism) [3].

Some of these mutation-related pathogenic processes, resulting from artificial selection have been investigated using computerized bioinformatics procedures. For example, mutations in the HIV Surface protein (gp120), and the host CD4 have been identified to be responsible for the translation of HIV infection to AIDS disease [4,5]. Sequence alterations in and outside the gp120 of HIV and SIV have helped define HIV tropism [4,6] and origins of the non-B HIV isolates found in American soldiers who were on Foreign Service [7]. Cross-Atlantic transmissions of HIV isolates have also been identified [4]. Additionally, evolutionary roadmaps of several other HIV, SIV and Influenza viruses as well as their hosts have been recognized [4,8,9].

Another pathogenic process, which resulted from artificial selection and has been evaluated using computerized bioinformatics procedures is the reduced functionalities (drug resistance) offered by peptide-based drugs (Enfuvirtide), the protein targets of pathogens including the five classes of HIV protein targets [4,10,11] and the proteins encoding the pathogens (ERG11 of *Candida albican*) [11,12]. Over 1000 proteins from pathogens have been investigated using these procedures. They include HIV Influenza virus, HSP, TNF, Oncogenes, etc. [13] as well as Ebola virus [14].

However, a lot other pathogenic processes need be studied. For example, it has been established that transition metal ions, including Cu^{2+}, Fe^{2+}, Zn^{2+}, Co^{2+}, Mn^{2+}, which also serve as co-factors for various proteins are known to be toxic when in excess. Studies have recognized that body cells (cytosol) take care of these excesses through procedures like uptake regulation, delivery, storage and detoxification. These are achieved by proteins called Cation Diffusion Facilitators (CDFs) [15]. Unfortunately, loss of function in these proteins (CDFs) has been recognized and has been attributed to mutations. The mutations include those in the protein metal-binding sites (D157A of YiiP). Others involve proteins that stabilize the structures of CDFs (E214A of ZitB, H237R and H280A of CzcD, respectively) [15].

A recent study has also shown that mutations in a human protein called Adenomatous Polyposis Coli (APC) are associated with Autism [16]. Similarly, it has also been authenticated that over 50% of human cancers are connected to loss of functions in the p53 protein resulting from mutations. A naive p53 protein has been identified to play a vital role in the transactivation necessary for pro-apoptotic functions. Unlike the wide type, p53 mutants are known to lack sequence-specific function [17]. Sequence alteration in the Beta subunit of the Haemoglobin (E6V) is known to precipitate Sickle Cell Anaemia [18]. Computerized bioinformatics procedures to assessing these bio-functionalities are needful.

Finally, toxicological properties of heavy metals have been found to be readable from the protein sequence information of their targets or those encoding them. For example, thousands of both human and microbial genes, which are found to be expressed by these metals including Arsenal, Cadmium, Mercury, Lead, Copper, Nickel, Manganese, and others have been investigated [19-23]. These studies had therefore explained functionalities of heavy metals in human [19-21], and microorganisms, during and after maturation. This has also helped the understanding of pathogenic processes, hence survival techniques of the metal-eating marine microorganisms that inhabit shipwrecks [22] and its oil-eating counterparts [23] hence their management.

Unfortunately, one surface protein (gp120) of HIV and SIV has over 180,000 sequences deposited in a database [24]. There are several other proteins that constitute the HIV. Each protein has vast mutants hence vast sequences resulting from natural and artificial selection. This applies to all pathogens and hosts. As a result, there are vast deposits of protein residues that need to be investigated. For example, there are 4611 number of peptides from one species of Plasmodium, which has about 728 species [25]. About 728 proteins have been identified including Circumsporozoite, and others [26].

Rational evaluations of disease progression (pathogenesis) as well as development of apparatuses for overcoming them from these large deposits of sequences can only effectively be carried out using computer-assisted bioinformatics procedures. Establishing a Center for these assessments is therefore required. Computerized bioinformatics procedures such as Digital Signal Processing (DSP)-based techniques [27] are recommended. They include Informational Spectrum Method (ISM) [4-12], Resonant Recognition Method (RRM) [13] and Continuous Wavelet Transform (CWT) [28]. RRM, which is versatile and shares same technicality with ISM is a Frequency component dependent technique that is processed using Discrete Fourier Transform (DFT). CWT is a Time-Series procedure, which might be improved upon. These DSP-based techniques are recommended because they are rational. They are information technology-based and engage sequence information. They do not employ sophisticated equipment, reagents and time. They also present biological characteristics in numerical terms; hence provide easy and accurate assessments [27].

These techniques have fetched several point-of-care biomedical devices that would simplify assessment of biological information for use by healthcare providers. The biomedical devices include Computer-Aided Drug Resistance Calculator [6], Computer-Aided Druggability Detector [28], Computer-Aided Pharmaco-Investigator [29,30], Computer-Aided Vaccine Potency Assessor (InnoCentive Award Winning Solution ID: 9933477) and Computer-Aided Drug Potency Decoder [31]. It has also fetched free online programs for designing therapies for Ebola Disease [32] and Phylogenetic investigations [33].

We have earlier emphasized that it is essential is to understand how to aggregate the contributions as false results is not admissible in human health [31].

Methods

Materials

The materials, which include sequences of proteins under investigation, are retrieved from the databases including [24]. Figure 1 is an example of a sequence (CAPAGFAIL) of HIV-1 Surface protein (UNIPROT ID: P04578, 218-226), which is known to bind to and interact with another protein HLA-Cw* 0102 [4,34]. Where only mutations are provided, mutated sequences are correspondingly constructed from the consensus sequences. Another material is the Amino Acid Scales [35]. The protein alphabetic codes, representing the amino acid sequences are converted into numerical sequences (signals) using Amino Acid Indices (AAIs) [35] involved.

Procedure

The recommended procedures for the Center, Informational Spectrum Method (ISM) [4-12], Resonant Recognition Method (RRM)

[13], and Continuous Wavelength Transform (CWT) [28] have already documented. ISM technique is briefly provided here though it is detailed [4-12].

Translation of the protein residues sequence into numerical sequences (signals) using appropriate amino acid scales: Here, the protein alphabetic sequences are interchanged with the corresponding numerical values of the Amino Acid Indices [35]. This presents the bio-functionalities under investigation as signals using the Amino Acid Scale utilized (Table 1 and Figure 1).

Amino Acid	EIIP Value	Amino Acid	EIIP Value	Amino Acid	EIIP Value	Amino Acid	EIIP Value
A	0.0373	Q	0.0761	L	0	S	0.0829
R	0.0959	E	0.0058	K	0.0371	T	0.0941
N	0.1263	G	0.05	M	0.0823	W	0.0548
D	0.0036	H	0.0242	F	0.0946	Y	0.0516
C	0.0829	1	0	P	0.0198	V	0.0057

Table 1: Protein Alphabetic codes and their corresponding Electron-Ion Interaction Potential (EIIP) Values.

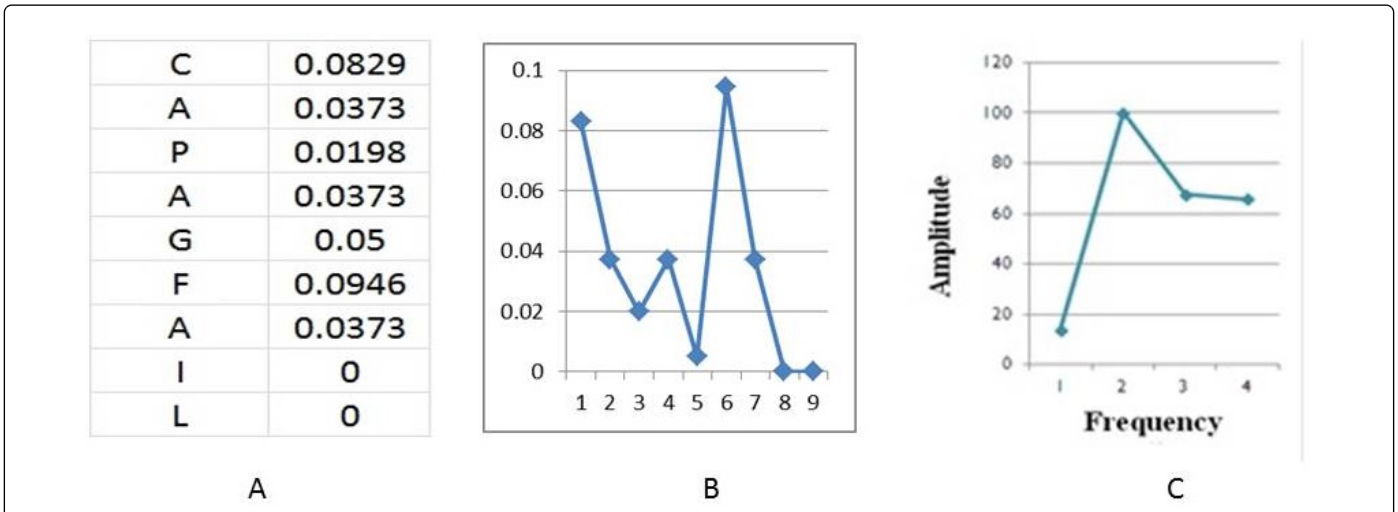

Figure 1: Translation Process of (A), the HIV-1 Surface protein (gp120, 218-226) peptide and numerical sequences into (B), Signal using EIIP and (C), the Informational Spectrum (courtesy [4]).

Processing of the signals using discrete fourier transform (DFT): The Signals are then decomposed using Discrete Fourier Transform to unveil the biological characteristics embedded in the proteins. The uncovered bio-functionalities are presented as plots, with y-axis expressing the magnitude of interaction as amplitude and the x-axis as the position of interaction.

Common informational spectrum: Accordingly, to the ISM procedure, proteins with common biological characteristics present maximum amplitude at a position of common interaction. In order to obtain a common position of interaction therefore, a point-wise multiplication is required. This position is called Consensus Frequency (CF).

By aggregating the contributions made by each sequence using the Amino Acid Indices involved, biological characteristics of the proteins under investigation are obtained. This way, pharmacological activities of drugs even those with a frightening structure are simply unveiled from the sequence information of these drug-proteins, protein targets or proteins encoding the drugs.

Results

ISM and RRM procedures have recorded successes not only in investigating bio-functionalities of over 1000 proteins, but in developing drugs, vaccines, and biomedical devices.

HIV pathogenesis

As preliminarily determined [4,5], the CCR5 HIV tropics (also called Macrophage-loving viruses), which predominate early stage of HIV pathogenesis (asymptomatic and sero-conversion) have weak affinity for the host CD4. During this phase, there is enough CD4 for the limited HIV to feed on. As time progresses and the infected individual is not treated, the pathogenic process proceeds to an intermediate stage. As the CD4 decreases, HIV modifies its bio-functionalities (structural and physio-chemical characteristics) necessary to enhance affinity for CD4. These modifications are expressed as sequence changes. These changes are essentially noticed in the V3 domain of the gp120. These mutations are responsible for the transformation of the less CD4-attractive CCR5 HIV tropics into highly CD4-attractive CXCR4 tropics (sometimes referred to as T-Cell Lymphocyte-loving). CXCR4 are known to dominate the later stage of the viral pathogenesis (Table 2).

Protein ID	Isolate	Binding Interaction %	Tropism	Protein ID	Isolate	Binding Interaction %	Tropism
P03377	BRU/LA1	84.77	CXCR4	P04583	MAL	29.21	CCR5
P03375	BH10	98.14	CXCR4	P04583	JH32	35.46	CCR5
P04578	HXB2	92.21	CXCR4	P12487	Z2/CDC-Z32	37.56	CCR5
P04582	BH8	82.28	CXCR4	Q9QSW7	V1850	35.26	CCR5
P04624	HXB3	96.55	CXCR4	Q9QB24	96CM-MP255	27.9	CCR5
P19551	MFA	100	CXCR4	Q9QB20	97ZR-EQTB11	46.19	CCR5
P03378	ARV2/SF2	65.01	CXCR4	Q9QBY2	96CM-MP535	12.36	CCR5
P19550	SF162T	41.07	CXCR4	P19550	SF162M	37.5	CCR5

Table 2: The Percentage levels of affinity between gp120 of 16 HIV isolates and host CD4 at the position of common interaction [4-7].

The study revealed that as the CCR5 viruses destroys and depletes the CD4, they mutate into CXCR4. This is in order to enhance their affinity with the CD4. By sustaining their grip and continuing to destroy the CD4, they erode the immune system, which in turn manifest as AIDS. This explained HIV pathogenesis under natural selection. Table 2 is the results of the ISM-based numerically derived contributions regarding binding interaction from 16 HIV isolates at the position of common interaction with the CD4.

Microbial drug resistance

HIV pathogenesis under artificial selection entails its attitude towards harmful environment such as drug pressure or host defence, etc. HIV undergoes series of mutations in its drugs protein targets in order to counteract the adverse effects of the drugs. Drug resistance arising from mutations in the HIV protein targets belonging to five classes of antiretroviral and an antifungal agent have been investigated using ISM procedure [4,10,11]. Table 3 is the results of the study using various Amino Acid Scales (AAS). Figures 2 and 3 are typically representations of the ISM-based analysis of reduced susceptibility to Bevirimat and Retalgravir, assessed using target proteins, Maturation and Integrase enzymes, respectively.

As shown in Table 3 and Figures 2-4, the differences between the IS of the susceptible strains (wild-type with the consensus sequence) and those of the mutants exposed from five classes of antiretroviral and an antifungal agent demonstrated different degrees of reduced susceptibilities at the position of common interaction (Consensus Frequency, CF). While Retalgravir and Bevirimat have their potencies reduced by 3.16 (Figure 2) and 5.42% (Figure 3), respectively, the Entry Inhibitor (Enfuvirtide) protein target displayed reduced susceptibility of 2.33%. Additionally, Lamuvidine and Darunavir showed resistances of 5.33 and 10.05%, each while the antifungal agent; Fluconazole expressed 0.7% from one mutant and using one AAI only (Table 3 and Figures 2-4)).

Drug	AAS	Susceptible strain	Resistant strain	Resistance
Bevirimat	EIIP	98.94%	93.52%	5.42%
Darunavir	WILM950103	100%	89.95%%	10.05%
Enfuvirtide	ROBB760104	100%	97.77%	2.23%
Lamuvidine	BEGF750103	200%	94.67	5.33%
Raltegravir	LIFS790103	100%	96.84%	3.16%
Fluconazole (antifungal)	EIIP	100%	99.30%	0.70%

Table 3: Resistance offered to an Antifungal and five classes of Antiretroviral Agents [4,10,11].

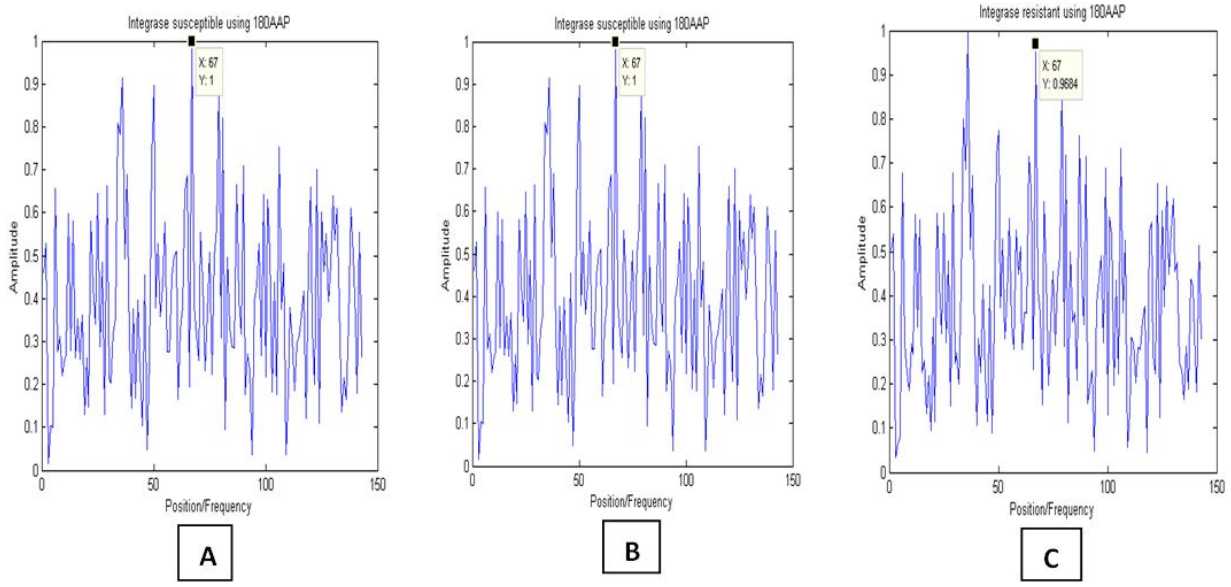

Figure 2: (A) Common Informational Spectrum (CIS) of Raltegravir susceptible and resistant sequences, (B) Informational Spectra (IS) of the susceptible sequence showing amplitudes 1 or 100%, and, (C) IS of the resistant mutant with amplitude of 0.9984 or 96.84% at the position of common interaction (position 67), signifying resistance of 3.16% as derived using Amino Acid Index, LIFS790103 [4,11,12].

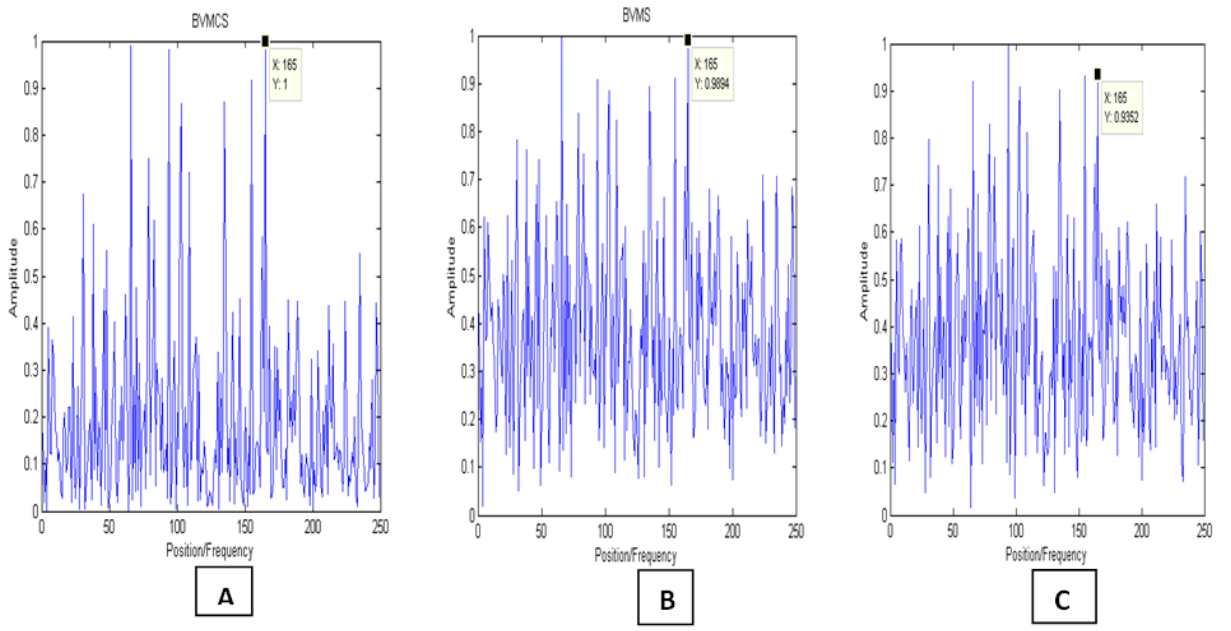

Figure 3: (A) Common Informational Spectrum of Bevirimat susceptible and resistant sequences, (B) Informational Spectrum (IS) of the susceptible sequence showing amplitudes 98.94% and, (C) IS of the resistant mutants (93.52%) at the position of common interaction (165), leaving a resistance of 5.42% using Amino Acid Index, EIIP [4,11,12].

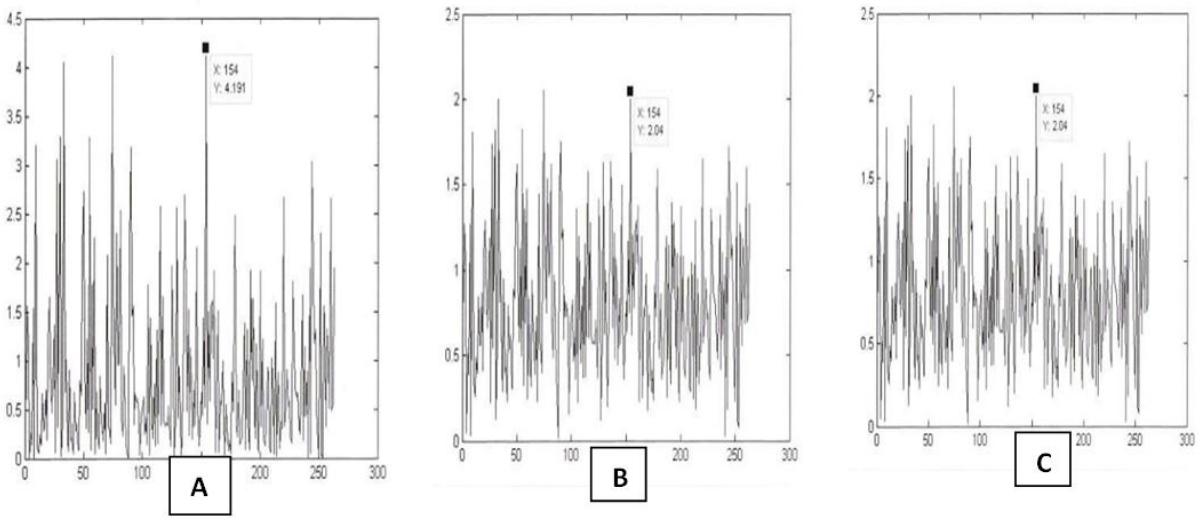

Figure 4: (A) EIIP-based Common Informational Spectrum (CIS) or point-wise multiplication of Fluconazole susceptible and resistant (K143R) sequences with an amplitude of 4.191, un-normalized, (B) Informational Spectrum of the Susceptible (amplitude 2.054, normalized to 100% for purpose of comparing with the Resistant sequence) and, (C) the Resistant sequences (amplitude of 2.04 normalized to 99.30%) leaving a resistance of 0.7% [11,12].

Evolutionary roadmaps

Another HIV pathogenic characteristics earlier studied using ISM procedure is the evolutionary roadmaps. The originality that exists between human and chimpanzee as earlier established using procedures like pollical distal phalanges [36] and DNA [37], was first re-ascertained using ISM (Table 4 and Figures 5). The CD4 of both human and chimpanzee maintained SPMBI at position 68, respectively. As shown in Table 4 and Figure 6, three species of another HIV hosts (monkey) including dancing, green and pig-tailed shared SPMBI at position 101(Frequency of 0.210). As recorded in Table 4 and Figure 7, an American isolate (CDC 451) shared same SPMBI (155) with two others from across the Atlantic (OYI, Gabon) and (Z6, Zaire). Similarly, two other American isolates SC and Z6/CDC-734 shared same SPMBI at positions 152 and 150 with two sets of African strains (96CM-MP535 and WMJ1) as well as (MAL and ELI). These are as shown in (Table 4 and Figures 5-8).

Common Position of Interaction	Host or Isolate (Origin) /magnitude of interaction	Host or Isolate (Origin) /magnitude of interaction	Host or Isolate (Origin) /magnitude of interaction
68 (Frequency of 0.141)	Human/72.35%	Chimpanzee/6.764	Nil
101 (Frequency of 0.210)	Monkey (Dancing)/65.92%	Monkey (Green)/76.99%	Monkey (pig-tail)/75.11%
155 (Frequency of 0.305)	OYI (Gabon)/100%	Z6 (Zaire)/74.43%	CDC 451 (US)/68.54
152 (Frequency of 0.209)	SC (US)/68.42%	96CM-MP535 (Cameroon)/54.99%	WMJ1 (Zaire)/48.90
150 (Frequency of 0.295)	MAL (Zaire)/64.45%	Z2/CDC-734 (US)/72.8%	ELI (Zaire)/63.28%
158 (Frequency of 0.311)	HIV-1 V1850 (Human)/57.93%	SIV MB66 (Chimpanzee)/69.28%	Nil

Table 4: Results of the shared Spectral Point of Maximum Binding Interaction demonstrating relationships by HIV/SIV isolates demonstrating cross-Atlantic transmission [4].

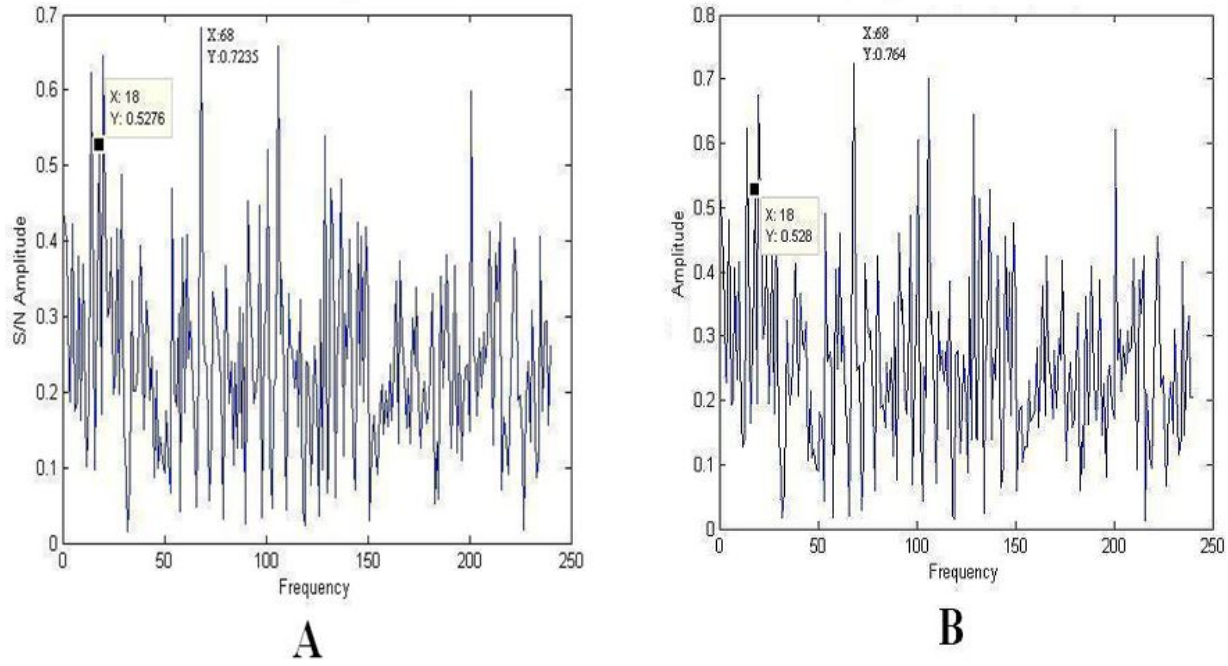

Figure 5: Informational Spectra of Human and Chimpanzee showing shared Spectral Point of Maximum Binding Interaction at position 68 symbolizing relationships with each other [4,6,7].

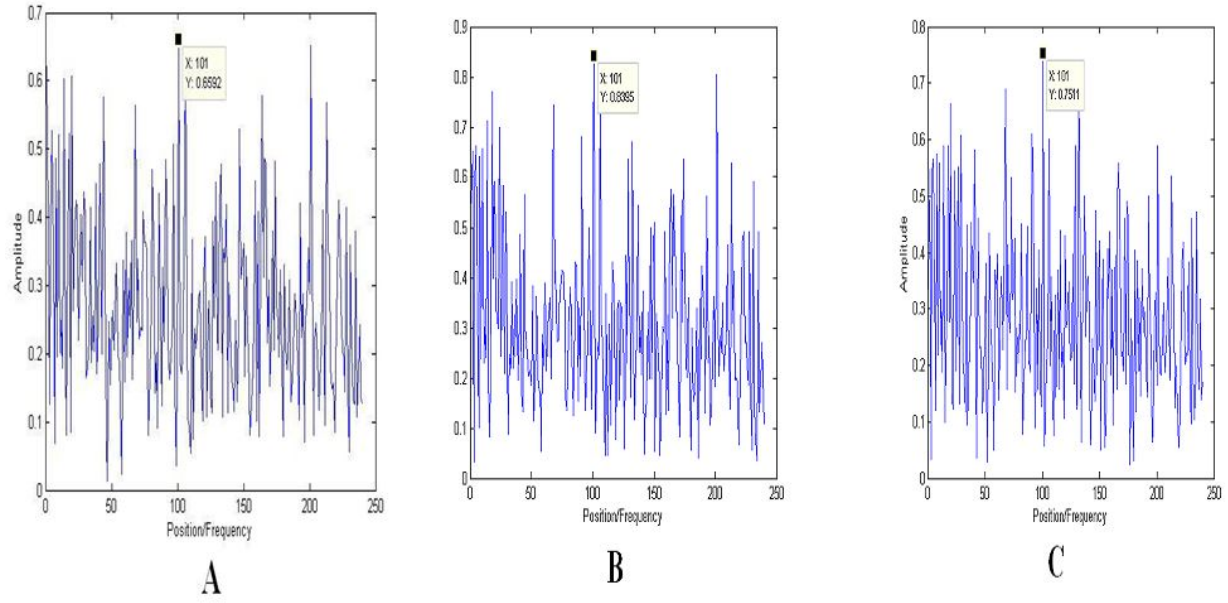

Figure 6: Informational Spectra of dancing, green and pig-tailed monkeys showing shared Spectral Point of Maximum Binding Interaction (SPMBI) at position 101, demonstrating relationship [4,6].

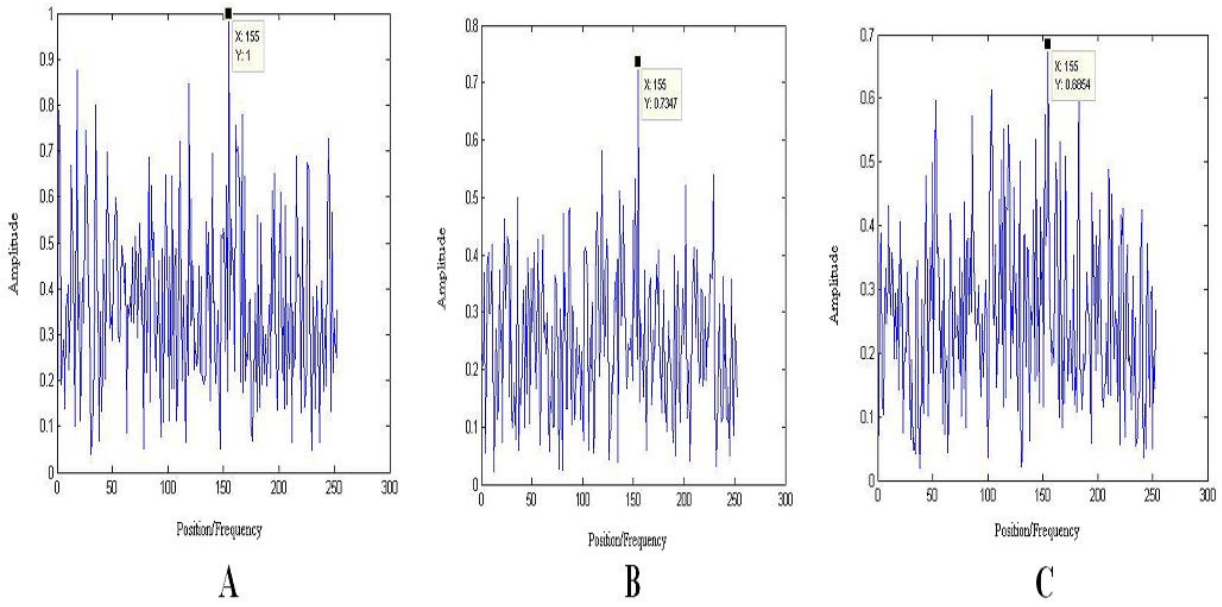

Figure 7: Informational Spectra of HIV isolates OYI, Z6 and CDC-451showing shared Spectral Point of Maximum Binding Interaction at position 155 signifying cross-Atlantic relationship [4,6,7].

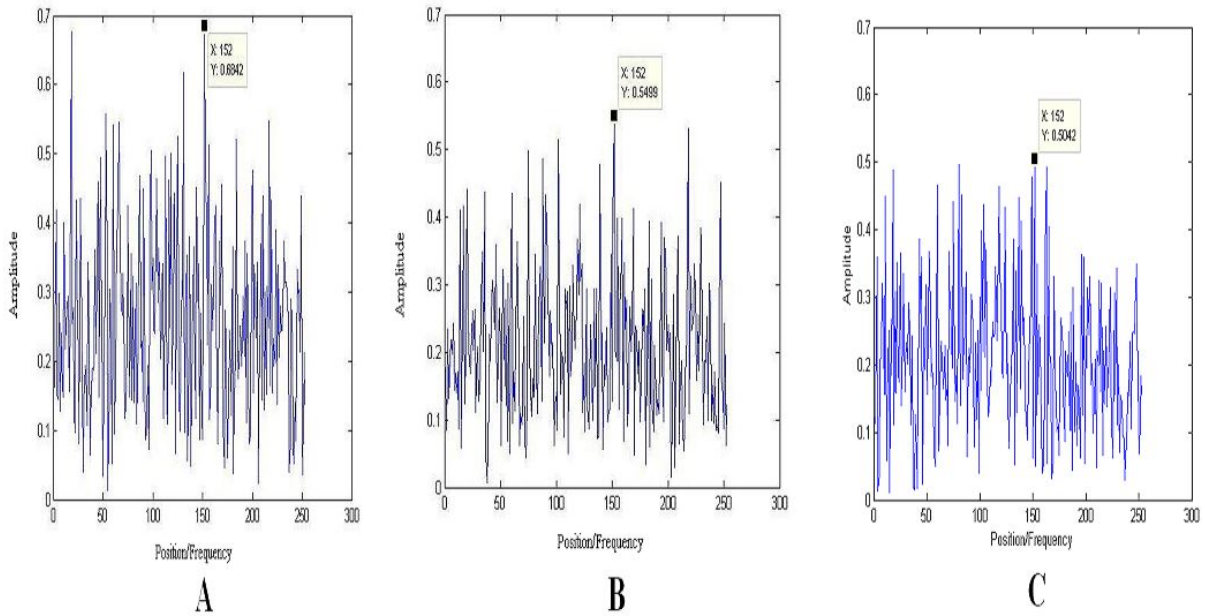

Figure 8: Informational Spectra of SC, 96CM-MP535 and WMJ1 showing shared Spectral Point of Maximum Binding Interaction at position 152 signifying trans-Atlantic relationship [4,6,7].

Preliminary understanding that HIV originated from the Chimpanzee was validated by this ISM-based procedure, which demonstrated that one human isolate (HIV V1850) and its chimpanzee counterpart (SIV MB66) shared a SPMBI at position 158 (Frequency of 0.311). The results of this preliminary study [4] is displayed in Table 4. Similarly, evolutionary roadmaps of several Influenza viruses have been studied [8,9].

This approach has also helps identify the origins of non-B HIV isolates found amongst American soldiers who were on Foreign Service [7]. In this study, two non-B HIV isolates (98US-MSC5007 and 98US-MSC5016) were obtained from American soldiers serving abroad and investigated. Non-B strains of HIV are not categorized as those found in America. Since they are found in soldiers who had served abroad, it became necessary to identify their origins and re-

route them. This action is envisaged to immensely assist in designing appropriate therapeutic interventions. Development of effective antiretroviral has been hampered by diversity and cross-typing. The study revealed that 98US-MSC5007 shares same SPMBI at position 44 with the Nigerian isolate (92NG083) while 98US-MSC5016 has similar SPMBI at 149 with the Zairean isolates, ELI, MAL.

Discussion

As already demonstrated in various studies [4-14,28-33], Digital Signal Processing-based techniques have presented themselves as powerful and reliable tools for not only assessing disease bio-functionalities but presenting them numerically as well as developing biomedical devices that would augment these assessments. As Discrete Fourier Transform-based techniques, their robustness is validated by their employment in delicate fields like Radar Technology, Speech Detector, and Image Processing [27]. Results obtained using these procedures have been found to be in accord with those clinically derived.

We have successfully demonstrated HIV and SIV pathogenesis, predicted their tropism, and determined their cross-Atlantic routes, evolutionary roadmaps and those of their hosts. We have also calculated resistance these pathogens offer to various antiretroviral agents and proffered biomedical devices. We have also determined the biological characteristics of over 1000 proteins, protein-targets of bioactive substances including HIV, Heat Shock Proteins, Oncogenes, Plasmodium, Ebola, etc. Evaluations made with these procedures are considered rational because expensive and sophisticated equipment, lengthy time are not engaged. They only engaged computerized program and sequence information.

Computerized and Bioinformatics-based programs remain the best approaches especially as vast protein sequences are involved. For example, a HIV/SIV protein (surface protein, gp120) has over 180,000 sequences deposited in a database [34]. However, there are several other proteins of the HIV and SIV. Similarly, plasmodium specie, *Plasmodium falciparum* has about 728 proteins that constitute 4611 peptides [26]. This vastness in the deposit of sequences with uncovered bio-functionalities applies to other diseases. As a result, it is impracticable to quickly assess these biological characteristics embedded in these sequences using clinical procedures.

Conclusion

Incorporating Digital Signal Processing techniques into the field of Bioinformatics has demonstrated applicability in areas such as Oncology, Neuro-biology, Cardiology, Pharmacology, Toxicology, etc. This applicability is highlighted in this study.

It has been identified that biological characteristics of bioactive agents are decipherable from their sequence information. This is because all bio-functionalities arising from diseases and activities of non-protein bioactive agents including drugs, vaccines, heavy metals, and others are made manifest in sequence information of their protein targets or proteins encoding them. These sequence information-based techniques described in this study present the uncovered bio-functionalities in numerical terms, making them better tools for accurate assessments. These techniques do not engage reagents, sophisticated equipment, and lengthy period of time. They engage protein sequence information and the Discrete Fourier Transform (DFT)-based Digital Signal Processing (DSP) technique such as Informational Spectrum Method. The DFT-based techniques are the basis for Radar technology that has served mankind in various capacities.

However, these Bioinformatics-based procedures engage vast sequence information. Each protein has so much deposit of sequences in various databases. This is worsened by the vast number of proteins from vast number organisms that need be investigated. Clinical procedures to assessing these biological characteristics embedded have become impracticable. In order to rationalize these assessments, these procedures need be computerized. Now that these computerized bioinformatics-based procedures are gradually getting incorporated into several disciplines, it is now necessary to establish a computerized bioinformatics-based Center that would engage multidisciplinary approach to investigations.

Strikingly, the reliability and sensitivity of the ISM-based procedure were demonstrated in these studies as there correlation between the findings made using ISM techniques and outcomes derived using clinical procedures. For example, ISM-based analysis of single point mutation (M162F) in the HIV isolate called SF that transforms the CCR5 tropic (SF162M) into CXCR4 tropic (SF162T) demonstrated 3.57% increase in affinity using only one AAS (Table 4) [4,5]. Additionally, our findings that two African isolates of HIV (OYI and Z6), which came from Gabon and Zaire, respectively shared resemblance in originality with the American CDC-451 is echoed by a preliminary outcome that identified an ancestral linkage [38]. Essentially, appropriate sequences and Amino Acid Scales must be engaged. Inappropriate employment of these parameters will be disastrous. To avert this, we have developed an approach for selecting appropriate sequences and Amino Acid Scales.

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