Zika Virus Viewed Through the Resonant Recognition Model. Unraveling New Avenues for Understanding and Managing a Serious Threat

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Abstract

Introduction: Zika Virus (ZIKV) infection is a major public health concern, affecting almost each country in the western hemisphere. A more than 20-fold increase in microcephaly risks is associated to ZIKV infection in pregnancy. A new vaccine is not expected before 2019, and alternative prophylactic and therapeutic approaches are encouraged. We expect that the Resonant Recognition Model, developed by Irena Cosic, might lay on the basis for an alternative approach to handle ZIKV.

Objective: We tried to identify the resonant frequencies associated to the ZIKV polyprotein and their use for an automatic taxonomy of different ZIKV strains. We put to test the hypothesis of interaction between ZIKV envelope protein and the AXL receptor, one of the plausible mechanisms proposed for ZIKV-associated microcephaly.

Results: Four relevant frequencies (f_{RRM}) were found in ZIKV polyprotein consensus spectrum. Corresponding four spectral amplitudes allowed separating African from Asian/American ZIKV isolates (k-means clustering). Peak 3 (f_{RRM}= 0.2754) and Peak 4 (f_{RRM}= 0.334) yielded a finer separation between Asian sequences and those from the current outbreak collected in 2015 (Asian/American). Consensus spectrum for pooled Dengue virus and ZIKV polyprotein sequences suggest that Peak 4 might be a specific hallmark of ZIKV. RRM results support the interaction between ZIKV envelope protein and AXL membrane receptor. The interacting frequency of f_{RRM}= 0.167 seems to be a sub-harmonic of Peak 4.

Conclusions: Resonant recognition model provides a plausible view of processes involved in the interactions of ZIKV with the human host, and is suggesting the exchange of electromagnetic radiation at the frequencies of 601.8nm (yellow light) and 1203.6 (near infrared) during ZIKV envelope protein with the AXL receptor in the human fetal tissue. This information might be relevant for alternative approaches to new therapeutic approaches to treat ZIKV-associated damage to newborns.

Keywords

Zika virus; AXL; Resonant recognition model; Flaviviridae

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1 Introduction

In 1947, Rhesus 766, a captive monkey in the Zika Forest of Uganda was detectedwith fever.Two days later, Rhesus 766, still febrile, was brought to the Rockefeller Foundation's laboratory at Entebbe and its serum wasintra-cerebrally inoculated into mice. After 10 days, all mice were sick, and a filterable transmissible agent, later named Zika virus (ZIKV), was isolated fromthe murine brains. In early 1948, ZIKV was also isolated from *Aedes africanus* mosquitoes captured in the Zika forest. In 1952, for first time, a case of human infection with Zika virus was documented in Uganda [1]. In 1964, Simpson provided the first well-documented report of human ZIKV disease (ZVD), narrating his own occupationally acquired Zika fever (ZF). Disease beganwith minor headache, followed the next day by maculopapular rash covering face, neck, trunk, and upper arms, and spreadingto palms and soles. The clinical picture also included fever, malaise, and back pain. By the evening of the second dayfever disappeared, the rash was receding, and by day three, he felt well. Rash completely disappeared over the next two days [2].

Until 2007, little attention was drawn to the ZVD. Its course was mild, and occurred mainly in a geographical region where malaria, HIV, tuberculosis, malnutrition and measles were the major reasons forinternational public health concern. According to some views, forest monkeys are the natural reservoir for the virus, which is transmitted among individuals by forest *Aedes* mosquitoes, with humans only as incidental hosts. Anthropological intervention apparently altered the sylvatic cycle of transmission: the virus mutated and started a dangerous spread around the planet. By 2007 it reached the Yap Island, in the Federate States of Micronesia, where 75% of their inhabitants fell infected.

At that moment (just tenyears ago!) premonitory were the words of Edward B. Hayes: "Fortunately, ZIKV illness to date has been mild and self-limited, but before West Nile virus caused large outbreaks of neuroinvasive disease in Romania and in North America, it was also considered to be a relatively innocuous pathogen" [3, 4].

After spreading to Malaysia and Cambodia, ZIKV finally reached South America by 2014, and by 2015 completed the circumnavigation of the planet reaching Cape Verde Islands in Africa.

Even when ZF still remains as a mild or even clinically silent entity, its most alarming feature is the proven association with certain neurological disorders, especially Guillain Barre Syndrome in adults and microcephaly in babies born to mothers infected during pregnancy (Figure 1).

From February 1st, 2016 until October 30th 2016, Zika virus was regarded by World Health Organization as a Public Health Emergency of International Concern (PHEIC) [5]. The figures of ZVDcases reached up to 6 digits globally [6, 7, 8], and the hypothesis of association of ZIKV with microcephaly as well as Guillain-Barre and ophthalmic anomalies is receiving mounting support [9]. In the Americas, all countries except Canada have been affected; in continental USA 5,575cases were reported up to September 30, 2017 [10].

ZVD is of particular concern among pregnant women. Recent reports suggest that Zika infection might increase the risk of brain malformation by a factor of 20-70 [11, 12].

A vaccine for ZIKV is not expected before 2019, and currently available antivirals are ineffective. There are worries regarding the efficacy of a ZIKV vaccine for curbing a ZVD pandemic. This justifies the search for alternative ways for ZIKV combat. As stated by Malone et al. [13]: "In the absence of currently available vaccines, the likely long timeline for vaccine development, and the open questions about the basic pathogenesis of Zika virus infection, parallel development of other prophylactics and therapeutics must be explored."

In developing countries, Bioinformatics is looming as one of the most promising and cost-effective research strategies. The application of mathematical models, the development of data mining and other similar approaches to the study of the huge genomic databases of public domain can devise new strategies aimed at understanding as well as proposing new ways of combating diseases.

Here we are showing how an approach based on the resonant recognition model can contribute to new proposals for facing ZVD.

The application of ideas and concepts from the Resonant Recognition Model (RRM) for infectious diseases control has been proposed for treating Ebola Virus Disease [14] as well as for malaria [15, 16]. Experimental evidence supporting the resonant exchange of electromagnetic energy as a way of interaction between proteins and their receptors, substrates and regulators (as postulated by RRM) is ample [17, 18 19], ideas based on this approach might propose new therapeutic ways to treat ZVD.

The existence of a mouse model for ZF [20], as well as the possibility to apply affordable low power radiation sources (e.g. LED´s [14]) might provide support to new strategies based on RRM. Drug design based on RRM has also suggested as an alternative way for treating different diseases, as some types of cancer [21].

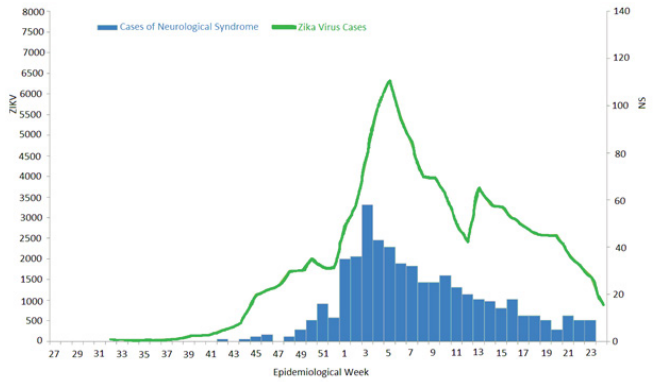

Figure 1: Cases of Neurological Syndrome and suspected and confirmed Zika virus disease cases by epidemiological week as reported for Colombia, 2015-2016. Modified from [4]

The main postulate of the RRM is that proteins do recognize their substrates/and receptors via exchanging electromagnetic radiation [17, 18, 19]. This process follow a resonant mechanism, and the exchanged energies are in the range of 10^{-20}—10^{-18} J (0.1—10 eV) [22].

A key aspect of the RRM approach is to identify the resonant frequencies involved. For it, one or various proteins that are determinative for fulfilling a given function were analyzed. As result of RRM analysis relevant frequencies as well as putative interactions might be identified. Below, a group of proteins related to ZIKV infection have been submitted to RRM analysis. Our results point to the plausibility of RRM as a way to understand some of the ZIKV mechanisms and, hopefully, to devise new therapeutic strategies.

2 Methods

2.1 Sequences

Flaviviridae polyproteins

Zika and other arboviruses´ genomes contain a coding region for a polypeptide which is processed into structural capsid, premembrane/membrane, envelope and non-structural proteins [6, 7, 8]. The following ZIKV full polyprotein sequences were downloaded from GenBank database (as translated into amino acid sequences from original full genome RNA sequences; Table 1).

They corresponded to the full list of ZIKV polyprotein sequences available at GenBank up to February 2016 [23].

The following polyprotein sequences from dengue virus were also downloaded:

P27909 (POLG_DEN1B)

P17763 (POLG_DEN1W)

P27912 (POLG_DEN1A)

P14337 (POLG_DEN28)

P29991 (POLG_DEN27)

2.2 Envelope Protiens

ZIKV envelope protein plays an important role in viral infection. It has been associated to functions such as fusion of virus membrane with host endosomal membrane, host-virus interaction, viral attachment to host cell, viral penetration into host cytoplasm, and virus entry into host cell [8].

The following six ZIKV envelope sequences were studied:

W8QFD5 – W8QFD5_ZIKV

W8R1N8 – W8R1N8_ZIKV

W8Q6P9 – W8Q6P9_ZIKV

W8Q6P1 – W8Q6P1_ZIKV

W8QFC5 – W8QFC5_ZIKV

W8QIQ1 – W8QIQ1_ZIKV

Each sequence contained 251 AA. Mutations were found in 12 different positions (8%).

Table 1: ZIKV polyprotein sequences analyzed in present study.

Accession Number	Country	Year of Collection
LC002520	Uganda	1947
HQ23449	Malaysia	1966
HQ234500	Nigeria	1968
KF383116	Senegal	1968
KF383115	CAR	1968
HQ234501	Senegal	1984
KF268948	CAR	1976
KF268949	CAR	1980
KF268950	CAR	1980
KF383117	Senegal	1997
KF383118	Senegal	2001
KF383119	Senegal	2001
EU545988	Micronesia	2007
JN860885	Cambodia	2010
KU681082	Philippines	2012
KU681081	Thailand	2014
KJ776791	Polynesia	2015
KU365779	Brazil	2015
KU365778	Brazil	2015
KU365777	Brazil	2015
KU3657780	Brazil	2015
KU312312	Suriname	2015
KU501215	P. Rico	2015
KU509998	Haiti	2014
KU321639	Brazil	2015
KU527068	Brazil	2015
KU647676	Martinique	2015
KU501216	Guatemala	2015
KU501217	Guatemala	2015
KU707826	Brazil	2015

Axl

The tyrosine kinase Axl protein is a cell surface receptor. Experimental evidence suggest that Axl is a strong candidate for ZIKV infection target [24].

The six following Axl sequences were downloaded:

NM_001278599

NM_001699

NM_021913

NM_001190974

NM_001190975

NM_009465

Resonant recognition model

The primary amino acid sequence was transformed into a numerical sequence following the Resonant Recognition Model (RRM) methodology [17]. Each of the 20 amino acids in the entire sequence was assigned an electron-ion interaction potential (EIIP) value (Table 2)

The obtained numerical sequence was treated as a time series. Power spectrum was obtained for each sequence using the freely available SciLab cross-platform numerical computational package (https://www.scilab.org/). For finding the consensus spectrum, all the spectral vectors were submitted to scalar cross multiplication. The obtained product is considered as the consensus spectrum. Relevant peak(s) are taken as important frequencies associated to resonant processes associated with the analyzed sequences.

Table 2: EIIP values for each amino acid [17] .

Amino Acid	EIIP
S	0.0829
T	0.0946
Q	0.0761
Y	0.0516
G	0.005
A	0.0373
V	0.0057
L	0
I	0
C	0.0829
M	0.0823
P	0.0198
F	0.0946
W	0.0548
K	0.0371
D	0.1263
E	0.0058
R	0.0959
H	0.0242
N	0.0036

EIIP represents the average energy state of all of the valence electrons associated with that amino acid.

The RRM frequency (f_{RRM}) was converted to a true electromagnetic frequency by determining the appropriate wavelength (λ) using the expression proposed by Cosic [17]:

$$f_{RRM} = 201/\lambda$$

Statistical processing

Procedures included cluster, regression and correlation analysis.

3 Results

3.1 RM Analysis of ZIKV Full Genome Polyproteins

The consensus spectrum corresponding to the 30 known polyprotein sequences available at GenBank in February 2016 allowed to identify four distinct peaks at RRM frequencies (f_{RRM}) of 0.038 (Peak 1), 0.125 (Peak 2), 0.2754 (Peak 3), and 0.334 (Peak 4) (Figure 2). These peaks could be regarded as the main candidates for further RRM analysis. These frequencies most likely correspond to wavelengths of 5289.5 nm (mean infrared) for Peak 1; 1608 nm (near infrared) for Peak 2; 729.9 nm (visible red light) for Peak 3, and 601.8 nm (yellow color) for Peak 4.

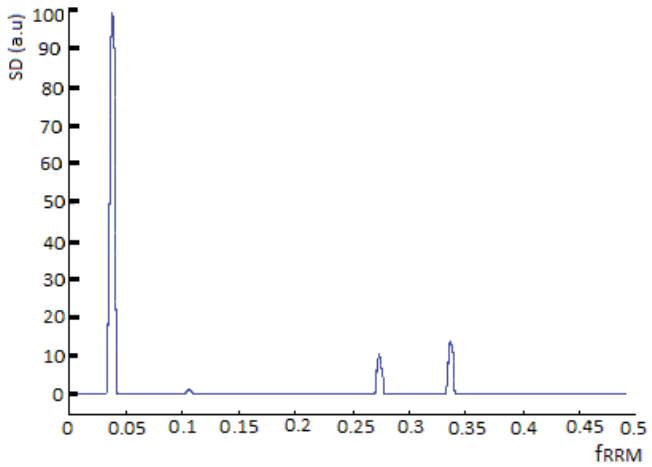

Figure 2: Consensus spectrum corresponding to the 30 ZIKV full genome sequences known up to February2016.Note the four distinct peaks encountered: Peak 1 (f_{RRM} =0.038), Peak 2 (f_{RRM}= 0.125), Peak 3 (f_{RRM}= 0.2754) and Peak 4 (f_{RRM}= 0.334).

3.2 Spectral Density of Each Frequency and ZIKV Evolution

According to the RRM, increase or decrease in RRM spectral amplitude is regarded as an enhancement in the related activity/ interaction. Thus we are analyzing in this section possible implications of spectral density values corresponding to a group of 21 ZIKV polyprotein sequences

With the aim of associating spectral density values of each peak to the origin of ZIKV strains, data were submitted to multivariate cluster analysis (k-means clustering), using the amplitude of each spectral peak as the four predictive variables. The following two clusters were obtained:

Cluster Number 1, containing 10 strains

- Malaysia (1966)
- Nigeria (1968)
- Senegal (1968)
- Central African Republic (1968)
- Senegal (1984)
- Central African Republic (1976)
- Central African Republic (1980)
- Senegal (1997)
- Senegal (KF383113; 2001)
- Senegal (KF383114;2001)

Cluster Number 2, containing 11 strains

- Micronesia (2007)
- Cambodia (2010)
- Polynesia (2015)
- Brazil (KU365771; 2015)
- Brazil (KU365772; 2015)
- Suriname (2015)
- Puerto Rico (2015)
- Haiti (2014)
- Brazil (KU527061; 2015)
- Martinique (2015)
- Guatemala (2015)

This statistical classification based on RRM analysis is in agreement with the view of classifying all African sequences and the Malaysian 1966 isolate as "African" [23], whereas the American sequences of current outbreak are similar to the "Asian" lineage [6, 8].

3.3 Relation of Different Peaks to ZIKV Classification

Correlation analysis revealed that Peak 1 and Peak 2 tend to be lower in Asian/American isolates, whereas Peak 3 and Peak 4 are increased among Asian/American ZIKV Polyprotein sequences (Table 3).

3.4 Possibility to Discriminate Between Asian and American ZIKV Lineages

Inspection of data from Asian and American ZIKV Polyprotein strains suggested that peaks P3 and P4 seem to increase among the strains from the current epidemic as compared to the Asian outbreaks from2007-2010. It is possible that the virulence of Asian/ American strains is associated to some of these two peaks.

In order to reveal possible numerical discrimination capability, Asian and American ZIKV Polyprotein sequences were submitted to cluster analysis this time using amplitudes of Peak 3 and Peak 4 as predicting variables.

K-means clustering reveled the following two clusters:

Cluster Number 1, containing 2 cases

- Micronesia (2007)
- Cambodia (2010)

Cluster Number 2, containing 8 cases

- Polynesia (2015)
- Brazil (KU365771; 2015)
- Brazil (KU365772; 2015)
- Suriname (2015)
- Puerto Rico (2015)

Table 3: Significant correlations between ZIKV Polyprotein consensus spectrum peaks and their relation to classification (African corresponds to class 1 whereas Asian/American corresponds to class 2).

	P2	P3	P4	CLASS
P1	0.45		-0.54	-0.56
P2		-0.63	-0.44	-0.93
P3			0.63	0.75
P4				0.57

- Haiti (2014)
- Brazil (KU527061; 2015)
- Martinique (2015)
- Guatemala (2015)

Plausibly, the Polynesia 2015 isolatewas grouped with other American sequences from the current outbreak, but distinguished from the Cambodian and Micronesian strains from previous outbreaks [23].

3.5 Relation to Other Flaviviruses

A consensus spectrum was obtained for a set comprising five dengue virus and 9 ZIKV polyprotein sequences. The consensus spectrum is represented in figure 3. Surprisingly, three of the four peaks found for ZIKV are preserved in this consensus spectrum. Apparently, Peak 4 is negligible, suggesting that this peak might be more specific for ZIKV, whereas Peak 1, Peak 2 and Peak 3 correspond to mechanisms that are common to other flaviviruses.

3.6 Exploring Possible Interaction Between Zika Envelope Protein and Tyrosine Kinase Receptor Axl.

Axl has been suggested as a strong candidate receptor to ZIKV envelope protein during infection, in particular during fetal infection leading to microcephaly [24].

One of the keys postulates of the resonant recognition model proposed by Cosic states that interacting molecules „communicate“ with each other i.e. recognize each other at a distance, on the basis of the same characteristic frequency but opposite phases at that frequency. This key aspect of RRM has found experimental confirmation during the study of cross reactivity of certain antibodies: significant cross reactivity to the polyclonal antibodies raised against peptides which share at least one Characteristic frequency and phase at a given frequency has ben be observed [17]. This criterion has been used to determine whether two proteins should interact, as it was shown recently for putatively interacting Plasmodium proteins [16].

Based on the idea that, interacting proteins share a common frequency in the consensus spectrum as well as opposite phases, we tried to test the hypothesis of Axl as a receptor for ZIKV, via RRM analysis of the interaction between ZIKV envelope protein and the Axl protein.

In Figure 4, the consensus spectrum for ZIKV envelope protein and AXL is represented. Peaks appeared at and at f_{RRM}=0.072. Curiously, the main peak at f_{RRM}= 0.167 seems to appear as a sub-harmonic of Peak 4 (0.334/2=0.167).

A phase shift of 176° (0.978π, very close to the opposite phase condition) was found between ZIKV envelope and AXL, thus supporting an interaction between both proteins (Figure 5). The interacting RRM frequency of 0.167 corresponds to a wavelength of 1203.6 nm (near infrared).

4 Discussion

The application of a new, now widely accepted method requires a cautious approach, since prediction of such a method cannot be taken for granted. In our view, first we need to search for the plausibility of obtained data using the innovative RRM approach. Briefly, it can be commented that our previous report on a small sample of ZIKV envelope proteins, detected a major peak at position 0.295 (as evident from Figure 1 of that paper [25]). This frequency was found by Veljkovic et al. [26] to be the main RRM frequency, as they used a larger sample of sequences.

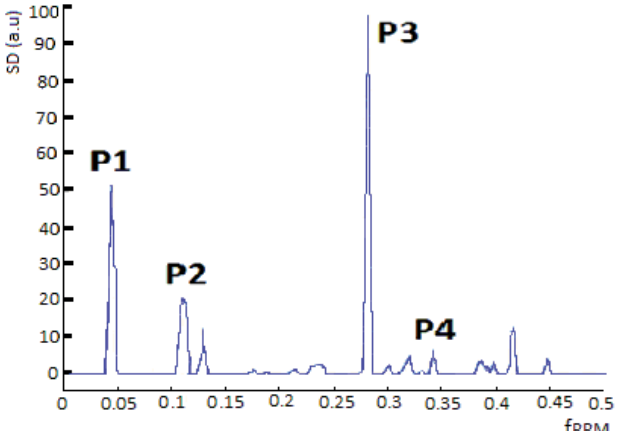

Figure 3: Consensus spectrum for pooled polyprotein sequences from five dengue viruses and nine ZIKV isolates. Peaks 1, 2 and 3 are prominent, whereas Peak 4 is barely present.

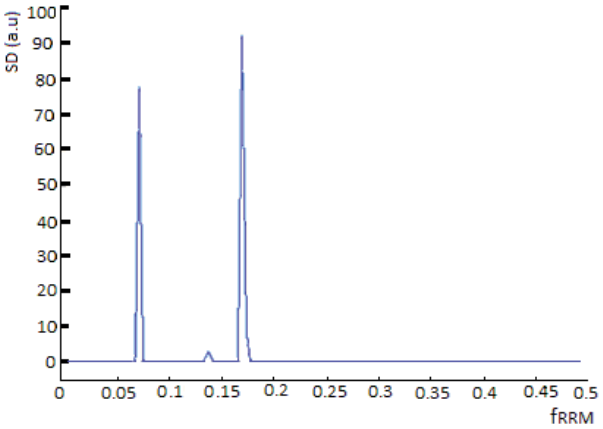

Figure 4: Consensus spectrum for the five ZIKV envelopesequences and six AXL sequences. Note a prominent peak at f_{RRM}=0.167and another peak at f_{RRM} =0.072.

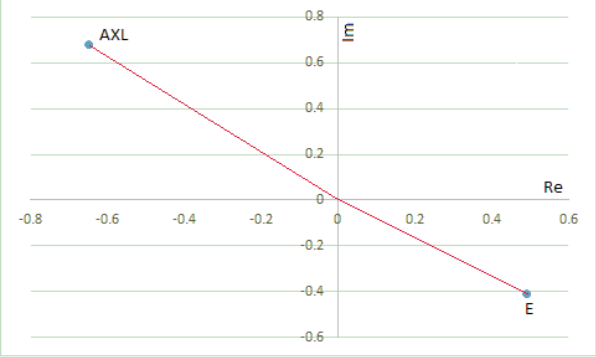

Figure 5: Phase values for ZIKV envelope protein (E) and human Axl receptor protein at f_{RRM}= 0.167. A phase shift of 176° (0.978π) was obtained.

In the present study, we are using a standard freely available program for spectrum determination, and the lack of an *ad hoc* package for RRM analysis could make our results incompatible with mainstream research in this area. Fortunately, this does not seem to be the case.

In a recent review, Cosic et al. [27] provided a detailed account of different biological processes associated to different RRM

frequencies. Comparing the frequencies described in this work with those described by Cosic et al. suggests the following:

The peak P1 at 0.038 is closely related to the frequency of 0.039, corresponding to IL-1, a protein involved in cell recognition, cell immunity and inflammation. As it is well known, these processes are common to flavoviruses invasion.

Peak P2 (0.125) is associated to myxoma viral activity (0.115) and is in a RRM frequency region associated to viral and bacterial infection processes [28].

Peak P4 at 0.334 is shared by several plasmodium proteins and apparently is associated to pathogen association to the cell membrane. Notice-worth is that Peak 4 seems to be specific for ZIKV and not to other flaviviruses, and microcephaly has been documented as associated to ZIKV and not to dengue virus.A sub-harmonic of this peak (0.167) has been shown here to correspond to a resonant interaction between ZIKV envelope protein and Axl. The resonant frequency of 0.167 corresponds to the DNA binding/ regulation region. As it has been reported, Axl dose dependently and specifically enhances NF-kB DNA-binding activity [29].

The common peak between AXL and ZIKV envelope protein at 0.072 is closely related to the peak at 0.07 reported for neurotoxins, and might reflect the interaction of ZIKV with neural tissue.

These reasons, added to the fact that these peaks were useful for discriminating between ZIKV strains of different origin do support the plausibility of RRM analysis for understanding molecular mechanisms involved in ZVD.

This report seems to be the first wide-range RRM study of Zika virus polyprotein. Two previous papers related to ZIKV envelope proteins were published recently [25, 26].

The study of 30 polyprotein ZIKV sequences allowed identifying four peaks. The peaks properly allowed to numericallydistinguish between African and Asian/American ZIKV isolates, and this support the idea of a functional role for corresponding electromagnetic frequencies.

Peak 3 and Peak 4, however, seemed to be more parsimonious in discriminating between Asian strains and those from current epidemic. The fact that Peak 4 is barely present in a consensus spectrum of polyproteins from a mixed *flaviviridae* pool including ZIKV and dengue viruses suggests that f_{RRM}= 0.334 (601.8nm) is specifically associated to ZIKV activity and must be a subject of future studies of ZF both *in silico* and *in vitro*. The fact that ZIKV envelope and human AXL receptor apparently recognize each other at a sub – harmonic frequency of Peak 4 adds further plausibility to the idea of this peak as a hallmark of ZIKV specific activity.

Based on RRM it is possible to design specific peptides or suggest a low power monochromatic radiation protocol. The availability of a murine model for ZVD provides the opportunity for experimental validation of proposed interventions [20].

5 Conclusion

The application of RRM analysis to ZIKV allowed identifying four candidate resonant frequencies that yielded a plausible discrimination between African and Asian/American ZIKV lineages. Association between ZIKV envelope protein and human AXL receptor was supported by RRM, since interaction met all theoretical requirements defined for an interaction between two proteins (sharing a common frequency and resenting opposite phases). Peak 4 at electromagnetic wavelength of λ=601.8nm seems to be the most parsimoniously associated to ZIKV activity. Overall, this study illustrates how a combination of ideas inspired in biophysical modeling and translational bioinformatics can lead to new insights to this serious public health threats.

6 Acknowledgements

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7 Author Contribution

Both authors were included in all phases of preparing this article and final proof reading before sending to print it.

8 Conflict of Interest

none declared.

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