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Analysis of Influenza A viruses using the resonant recognition model

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Abstract

Bird flu (*Avian influenza*) and human flu are both caused by Influenza A viruses, but they differ significantly in their host adaptation, transmission and severity. Here, we have used the Resonant Recognition Model (RRM), which is innovative approach using knowledge from quantum physics, biochemistry and mathematics, capable to analyse interactions between proteins and their targets, including other proteins, DNA, RNA, or small molecules. Using the RRM model we have identified different characteristics for different types of flu viruses, and we have found that there are three groups of flu viruses with completely different interactions with host cells receptors. Such finding can provide explanation why different flu viruses can interact only with specific hosts and why there is extremely low cross infection between different species, in particular between birds and humans.

Keywords: Influenza A; Birds Flu; Human Flu; Resonant Recognition Model; Molecular Modelling.

1. Introduction

Flu is an infectious disease caused by influenza viruses. Bird flu (avian influenza) and human flu (seasonal influenza) are both caused by Influenza A viruses, but they differ significantly in their host adaptation, transmission and severity. While human flu spreads easily between people, bird flu is highly adapted to birds and other animals and only rarely infects humans. Influenza A virus circulates in humans and causes seasonal epidemics and are primarily transmitted through respiratory droplets from coughing and sneezing. Transmission through aerosols and surfaces contaminated by the virus also occur.

Avian influenza, also known as avian flu or bird flu, is also disease caused by the influenza A virus, which primarily affects birds, but can rarely affect mammals including humans [1]. Wild aquatic birds are the primary host of the influenza A virus, which is continually present in many bird populations [2-3].

Influenza A is RNA virus with a genome comprising a negative-sense RNA segmented genome that encodes for 11 viral genes [4]. There are two proteins on the surface of the influenza A viral envelope: hemagglutinin and neuraminidase [5]. These proteins are the major antigens of the influenza A virus.

Subtypes of influenza A are defined by the combination of the antigenic viral proteins hemagglutinin (H) and neuraminidase (N) in the viral envelope. For example, H1N1 combination designates subtype that has type-1 hemagglutinin (H) protein and type-1 neuraminidase (N) protein [6]. Almost all possible combinations of H (1 through 16) and N (1 through 11) have been isolated from wild birds [7].

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Influenza A virus subtype H5N1 is a subtype of the influenza A virus, which causes influenza (flu) predominantly in birds. Subtype H7N7 can cause influenza in poultry and can infect some mammals. The influenza A virus subtypes in circulation among humans are H1N1 and H3N2 [5,8].

All influenza A virus strains need sialic acid as receptor to connect with host cells. There are different forms of sialic acids which have different affinity with influenza A virus variety. This diversity is an important fact that determines which species can be infected [9]. When a certain influenza A virus is recognised by a sialic acid receptor the cell tends to endocytose the virus, so the cell becomes infected.

There are a few factors that generally prevent the avian flu from causing epidemics in humans or other mammals [10-11]. One of them is that the H protein of avian influenza binds to alpha-2,3 sialic acid receptors (Figure 1), which are present in the respiratory tract and intestines of avian species, while human influenza H protein binds to alpha-2,6 sialic acid receptors (Figure 1), which are present in the human upper respiratory tract [12-13]. The presence of both alpha-2,3 and alpha-2,6 sialic acid receptors in pig tissues allow for co-infection by avian influenza and human influenza viruses. This susceptibility makes pigs a potential "melting pot" for the reassortment of influenza A viruses [14].

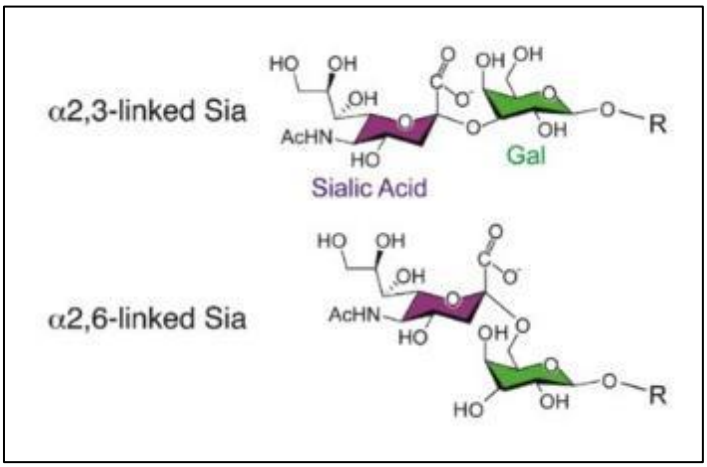

Figure 1 Sialic acid receptor structures: alpha-2,3 sialic acid receptor and alpha-2,6 sialic acid receptor.

We have used here the Resonant Recognition Model (RRM) to analyse characteristic parameters (frequencies) crucial for influenza A viral recognition and entry into the host cell. We have particularly analysed the differences between avian flu and human flu recognition and interaction with related versions of sialic acid receptors. Such findings could bring better understanding of species-specific flu infections, as well as to aid the potential design of anti-viral drugs.

2. Materials and Methods

Here, we have used the Resonant Recognition Model (RRM), which is innovative approach using knowledge from quantum physics, biochemistry and mathematics, capable to analyse interactions between proteins and their targets, including other proteins, DNA, RNA, or small molecules [15-26]. The RRM model is based on the findings that certain periodicities (frequencies) within the distribution of energy of delocalised electrons along protein backbone are critical for protein biological function and/or protein interaction with its targets. The RRM model has been extensively used, experimentally tested and extensively published in detail within the number of publications [15-35]. More details about the RRM model could be found in Appendix below.

We have applied here the RRM model on both avian and human flu virus's envelope proteins with the aim to find RRM characteristics of these proteins possibly related to their infectious functions. Using the RRM model, we have analysed both hemagglutinin (H) and neuraminidase (N) components of following influenza A subtypes: H5N1, H1N1, H3N2 and H7N7. All protein sequences used within this research are from UniProt database as follows:

Nineteen hemagglutinin H5 proteins: Q8QPL1, Q80A26, Q80A30, Q80A28, Q80A22, Q6DQ22, Q6DQ21, Q6DQ20, Q6DQ19, Q6J8E7, Q6DQ18, Q6DQ15, Q6J8F6, Q6DPZ9, Q2F4V2, P09345, Q9Q0U6, O89746, O56140.

Nineteen neuraminidase N1 proteins: Q8QPK2, Q809V0, Q809V4, Q809V2, Q809U7, Q6DPK2, Q6DPK1, Q6DPK0, Q6DPJ9, Q6J8D5, Q6DPJ8, Q6DPI6, Q6J8E4, Q6DPH9, Q2LFV4, Q710U6, Q9Q0U7, Q9WAA1, Q9W7Y7.

Twenty-seven hemagglutinin H1 proteins: Q289M7, B4URD6, A8C8J4, Q9WFX3, Q9WCD9, P03454, P03452, A4GCL9, A4GCI6, Q0HD60, A4GCK8, A4U6V2, A4U7A6, P18876, A4K143, Q9WCD8, A8C8W3, P03455, A4GBX7, P03453, P18875, A4GCJ7, A4GCH5, Q9WCE8, P26140, A3DRP0, Q07FI5.

Twenty-six hemagglutinin H3 proteins: P03438, P03437, Q91MA7, P03436, P03449, P17000, P19106, P03439, Q2ICR0, Q1PUD9, Q30NQ1, P03435, Q2RFA5, P26139, P03441, P26138, Q2VNF2, Q2VND2, P11133, P03441, Q2RCH5, P11134, Q38SQ8, P26141, P12589, O11283.

Fourteen hemagglutinin H7 proteins: P36346, P26101, P26094, P26096, P26097, P26098, P26103, P26095, P26099, P26102, P26100, Q6LEJ4, P09343, P09344.

Five neuraminidase N7 proteins: P18881, P88838, P08327, Q2VC95, Q0A2R1.

Twenty-nine neuraminidase N2 proteins: Q6XUE4, Q6XUD6, P06820, Q75VQ4, Q91MA2, Q6XUA7, P03473, Q6XTN2, Q6XTM7, P03471, P0DOF6, P03475, Q2ICQ7, P0DOF9, Q1PUD6, Q30NP8, P03482, Q2RFA3, Q09104, Q09105, Q9EA42, Q75VQ0, Q2VNF0, Q2VND0, P06818, Q2RCH3, Q38SQ5, O91744, O91745.

Using the RRM small molecule analysis (as described in Appendix), we also have analysed sialic acid receptors on both avian and human host cells with the aim of finding RRM characteristics of interactions between virus and host cells receptors.

3. Results

Using the RRM model, we have analysed both hemagglutinin (H) and neuraminidase (N) components of following influenza A subtypes:

- H5N1 as characteristic of avian influenza.
- H1N1 and H3N2 as characteristics of human influenza.
- H7N7 as influenza virus that can infect birds, some mammals, and humans but with different strengths.

We found that each of these three groups of influenza A viruses have different characteristic frequency indicating that they interact with host cells in separate ways. To find out the mechanisms of these interactions, we have also compared these characteristic frequencies with different types of structures of sialic acid receptors in different hosts.

3.1. Avian Influenza

As influenza A subtype H5N1 is predominant in birds, we have firstly analysed this subtype. When we compared 19 different H5 proteins (listed above), using the RRM model, it has been found that there is only one common frequency at f1=0.4912±0.0018, as presented in Figure 2a. Such common frequency characterises the common ability of H5 proteins to recognise and interact with receptor on avian host cells.

When we compared 19 different N1 proteins (listed above), using the RRM model, it has been found that there is only one common frequency at f2=0.4844±0.0022, as presented in Figure 2b. Such common frequency characterises the common function of N1 proteins. As characteristic frequencies for H5 and N1 are very close to each other, we propose that there is a possibility for N1 proteins to also recognise and interact with the same receptor on avian host cells.

As it has been known that the H protein of avian influenza A binds to alpha-2,3 sialic acid receptors (Figure 1), we have analysed both Sia and Gal elements of sialic acid receptor, using the RRM small molecule calculations. It is interesting that the characteristic frequency range for Gal only ($C_6H_3O_6$) of 0.4553-0.5000 is encompassing both characteristic frequencies for H5 and N1, as presented in Figures 2a and 2b with area highlighted in yellow. Such result indicates that in case of birds the initial recognition and interaction between influenza A subtype H5N1 is through Gal part of sialic acid receptor.

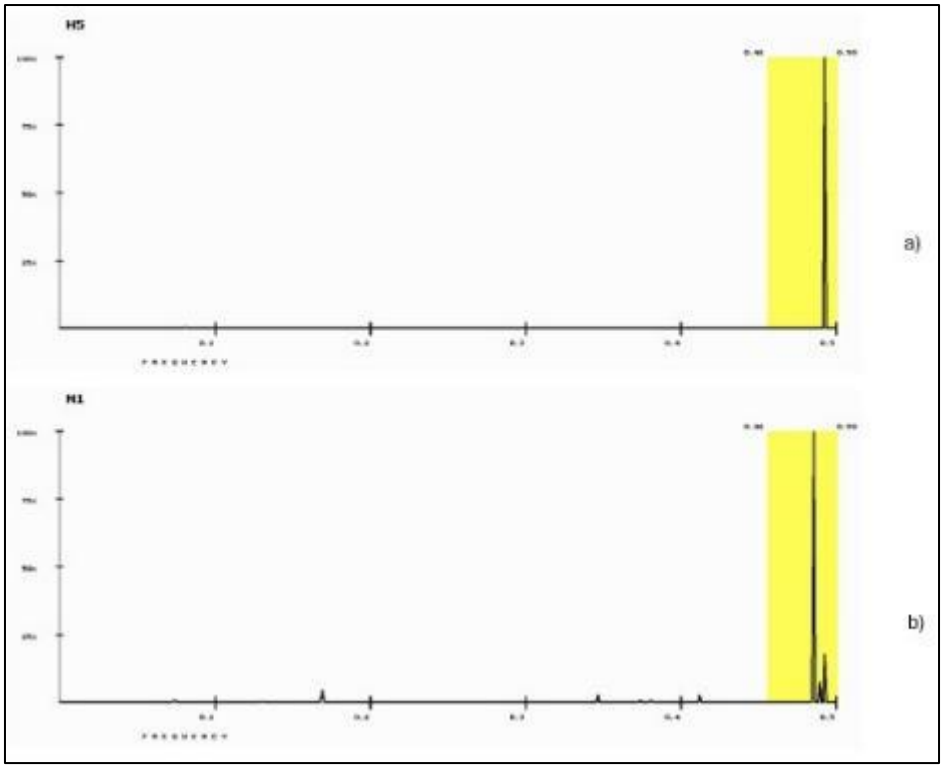

Figure 2 RRM characteristic frequency for H5 proteins at f1=0.4912±0.0018 (a) and RRM characteristic frequency for N1 proteins at f2=0.4844±0.0022 (b). The characteristic RRM frequency range 0.4553-0.5000 for Gal only is highlighted in yellow. It can be observed that frequencies f1 and f2 are close to each other and both are within frequency range of Gal, indicating possible interaction.

3.2. Human Influenza

We have also analysed influenza A subtypes H1N1 and H3N2, which are predominant in humans. When we compared 27 different H1 proteins (listed above), using the RRM model, it has been found that there is only one common frequency at f3=0.1826±0.0018, as presented in Figure 3a. Such common frequency characterises the common ability of H1 proteins to recognise and interact with receptor on human host cells. It is important to note that this frequency is completely different to characteristic frequency of H5 proteins. This result is indicating that H1 protein is interacting in different way than H5 protein with different structures of sialic acid receptors on host cells. This could explain why there is no significant influenza cross infection between birds and humans.

When we compared 26 different H3 proteins (listed above), using the RRM model, it has been found that there is only one common frequency at f4=0.1934±0.0018, as presented in Figure 3b. Such common frequency characterises the common ability of H3 proteins to recognise and interact with receptor on human host cells. As characteristic frequencies for H1 and H3 are very close to each other, we propose that H3 proteins can recognise and interact with the same receptor on human host cells.

As it has been known that the H proteins of human influenza A bind to alpha-2,6 sialic acid receptors (Figure 1), we have compared frequency ranges for both Sia and Gal elements of sialic acid receptor, as calculated using the RRM small molecule calculations. It is interesting that characteristic frequency range for Sia core ($C_9H_{17}N_1O_8$) of 0.1631-0.1933 is encompassing both characteristic frequencies for H1 and H3, as presented in Figures 3a and 3b with area highlighted in yellow. Such result indicates that in case of humans the initial recognition and interaction between influenza A subtypes H1 and H3 is through Sia core of sialic acid receptor (Figure 1), which is completely different entry point compared with H5N1 avian influenza A.

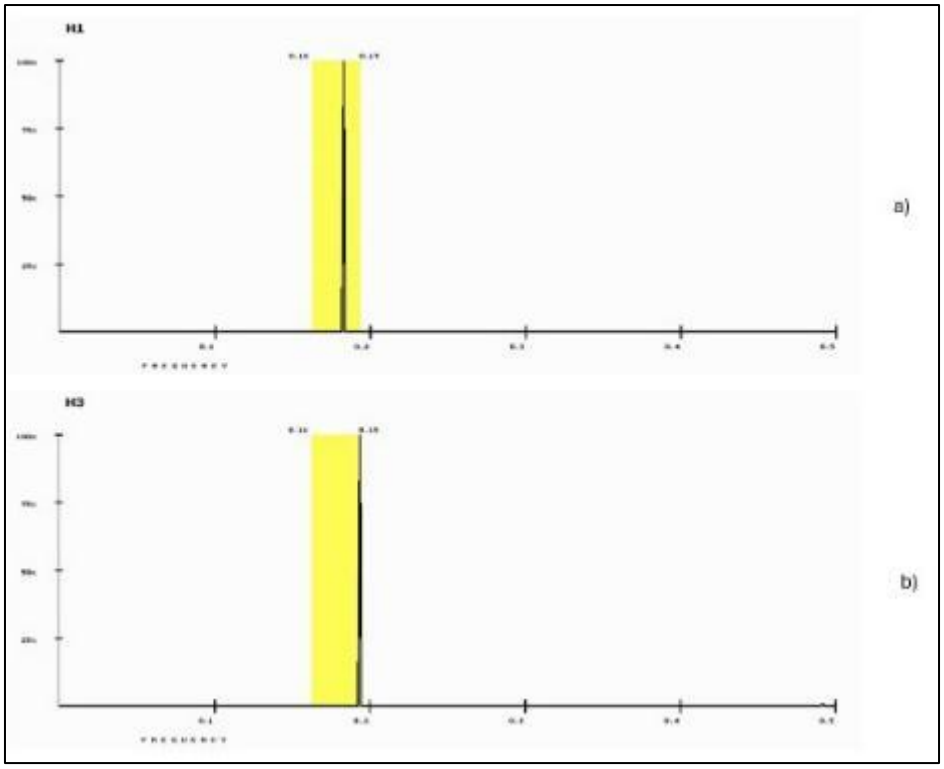

Figure 3 RRM characteristic frequency for H1 proteins at f3=0.1826±0.0018 (a) and RRM characteristic frequency for H3 proteins at f4=0.1934±0.0018 (b). The characteristic RRM frequency range 0.1631-0.1933 for Sia core is highlighted in yellow. It can be observed that frequencies f3 and f4 are close to each other and both are within frequency range of Sia indicating possible interaction.

3.3. Cross-Species Influenza

Influenza A subtype H7N7 can also infect some mammals and humans, but with lower strength. When we compared 14 different H7 proteins (listed above), using the RRM model, it has been found that there is one common frequency at f5=0.4307±0.0018, as presented in Figure 4a. Such common frequency characterises the common function of H7 proteins. When we compared 5 different N7 proteins (listed above), using the RRM model, it has been found that there is one common frequency at f6=0.4600±0.0022, as presented in Figure 4b. Such common frequency characterises the common function of N7 proteins.

As characteristic frequencies for H7 and N7 are close to each other, we propose that N7 proteins can also recognise and interact with the same receptor on avian and mammal host cells.

As H7N7 subtype infects both birds and mammals it seems that its entry does not depend on how Sia is linked to Gal, but it possibly recognises the whole Sia-Gal structure no matter of its structural connection. Thus, we have analysed complete Sia-Gal structure, using the RRM small molecule calculations and it has found that characteristic frequency range for Sia-Gal structure ($C_{15}H_{20}N_1O_{15}$) is 0.3973-0.4709 and is encompassing both characteristic frequencies for H7 and N7, as presented in Figures 4a and 4b with area highlighted in yellow. Such result indicates that in case of influenza A subtype H7N7 that infects birds and mammals the initial recognition and interaction with host cells is through the whole Sia-Gal sialic acid receptor (Figure 1).

In addition, we have analysed 29 N2 proteins of human influenza A subtype H3N2 (listed above), using the RRM model, and identified common characteristic frequency at f7=0.3975±0.0022. As there is possibility for some mutants of N1 and N2 subtypes to initiate entry into host cell [36], we propose that N2 may exhibit this possibility through interaction with the whole Sia-Gal sialic acid structure at the frequency f7, as presented in Figure 4c, while N1 may exhibit this interaction through Gal part of sialic acid structure at frequency f2 as explained above.

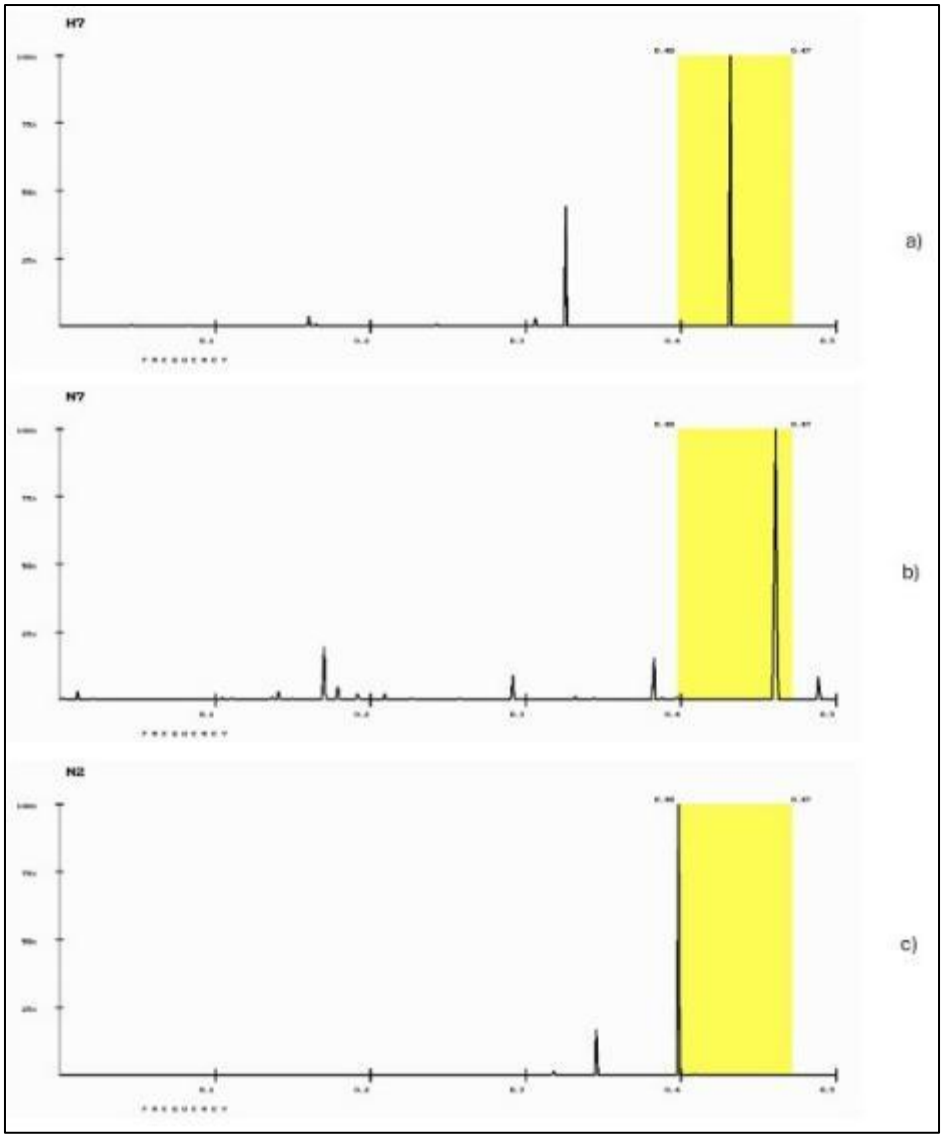

Figure 4 RRM characteristic frequency for H7 proteins at f5=0.4307±0.0018 (a) and RRM characteristic frequency for N7 proteins at f6=0.4600±0.0022 (b). The characteristic RRM frequency range 0.3973-0.4709 for Sia-Gal structure is highlighted in yellow. It can be observed that frequencies f5 and f6 are close to each other and both are within frequency range of Sia-Gal structure indicating possible interaction. RRM characteristic frequency for N2 proteins at f7=0.3975±0.0022 (c) is on the edge of Sia-Gal structure range indicating possible week interaction.

4. Discussion

We have analysed here the interaction of human and avian flu viruses with their respective cialic acid receptors. For that analysis we used the RRM model to identify characteristics specific for each interaction. It is interesting that we found three distinct characteristics (RRM frequency ranges) for different flu viruses: 0.4553-0.5000 mostly related to avian flu, 0.1631-0.1933 mostly related to human flu and 0.3973-0.4709 mostly related to both bird and mammal infections including human but with less severity. All these results are summarised in Table 1.

Table 1 List of RRM characteristic frequencies for different hemagglutinin and neuramidase proteins for different influenza A strains and different hosts indicating their possible receptors.

Protein	Host	Frequency	Possible Receptor
H5	Birds	0.4912	Gal (C6H3O6) 0.4553-0.5
N1	Birds/Human	0.4844	Gal (C6H3O6) 0.4553-0.5
H7	Birds, Mammals, Human	0.4307	SiaGalO (C15H20NO15) 0.3973-0.4709
N7	Birds, Mammals, Human	0.4600	SiaGalO (C15H20NO15) 0.3973-0.4709
N2	Human	0.3975	SiaGalO (C15H20NO15) 0.3973-0.4709
H1	Human	0.1826	Sia (C9H17NO8)0.1632-0.1933
H3	Human	0.1934	Sia (C9H17NO8)0.1632-0.1933

According to these results all analysed influenza A viruses can be classified into three groups according to receptor recognition and related to different infectivity and hosts:

Infecting birds only through recognition with Gal only. This group is very infectious and damaging (highlighted in blue in Table 1).

Infecting both birds and mammals through recognition with the whole Sia-Gal structure, possibly very infectious but not causing serious illness particularly in mammals and humans (highlighted in green in Table 1).

Infecting humans through recognition with Sia, very infectious and can cause serious illness in humans (highlighted in yellow in Table 1).

Having identified different characteristics for different types of flu viruses, we propose here that these three groups of flu viruses have completely different interactions with host cells receptors. Such finding can provide explanation why different flu viruses can interact only with specific hosts and thus there is extremely low cross infection between species in particular between birds and humans.

4.1. Contributions

Conceptualization, I.C., D.C. and I.L.; Methodology, I.C. and D.C.; Software, D.C.; Resources, I.L.; Writing—Original Draft Preparation—Review and Editing, I.C., D.C. and I.L.

5. Conclusion

We have used here our own unique Resonant Recognition Model (RRM) to analyse characteristic parameters (frequencies) crucial for influenza A viral recognition and entry into the host cells. We have particularly analysed the differences between avian flu and human flu viruses' recognition and interaction with related versions of sialic acid receptors. Using the RRM model we have identified different characteristics for three different types of flu viruses with completely different interactions with host cells receptors. Such findings can provide explanation why different flu viruses can interact only with specific hosts and why there is extremely low cross infection between different species, in particular between birds and humans. In addition, these findings could be base for the potential design of influenza A anti-viral drugs.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare they have no competing interests.

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References

[1] Avian Influenza A H5N1 - United Kingdom of Great Britain and Northern Ireland. www.who.int. Retrieved 16 May 2024.

[2] Li YT, Linster M, Mendenhall IH, Su YC, Smith GJ: Avian influenza viruses in humans: lessons from past outbreaks. British Medical Bulletin, 2019; 132(1), 81–95, doi:10.1093/bmb/ldz036.

[3] Joseph U, Su YC, Vijaykrishna D, Smith GJ: The ecology and adaptive evolution of influenza A interspecies transmission. Influenza and Other Respiratory Viruses, 2017; 11(1), 74–84, doi:10.1111/irv.12412.

[4] Samji T: Influenza A: understanding the viral life cycle. The Yale Journal of Biology and Medicine, 2009; 82(4), 153–159.

[5] Avian Influenza in Birds. U.S. Centers for Disease Control and Prevention (CDC), Retrieved 06 May 2024.

[6] Influenza Type A Viruses. U.S. Centers for Disease Control and Prevention (CDC), Retrieved 3 May 2024.

[7] FluGlobalNet – Avian Influenza. science.vla.gov.uk, Retrieved 5 June 2024.

[8] Current U.S. Bird Flu Situation in Humans. U.S. Centers for Disease Control and Prevention (CDC), Retrieved 22 May 2024.

[9] Racaniello V: Influenza virus attachment to cells: role of different sialic acids. Virology Blog, Retrieved 10 April 2019.

[10] Petric PP, Schwemmle M, Graf L: Anti-influenza A virus restriction factors that shape the human species barrier and virus evolution. PLOS Pathogens, 2023; 19(7), doi:10.1371/journal.ppat.1011450.

[11] Koçer ZA, Jones JC, Webster RG, Atlas RM, Maloy S: Emergence of Influenza Viruses and Crossing the Species Barrier. Microbiology Spectrum, 2013; 1(2), doi:10.1128/microbiolspec.

[12] Bertram S, Glowacka I, Steffen I, Kühl A, Pöhlmann S: Novel insights into proteolytic cleavage of influenza virus hemagglutinin. Reviews in Medical Virology, 2010; 20(5), 298–310, doi:10.1002/rmv.657.

[13] Kuchipudi SV, Nelli RK, Gontu A, Satyakumar R, Surendran NM, Subbiah M: Sialic Acid Receptors: The Key to Solving the Enigma of Zoonotic Virus Spillover. Viruses, 2021; 13(2), 262, doi:10.3390/v13020262.

[14] Steel J, Lowen AC, Compans RW, Oldstone MB: Influenza a Virus Reassortment. Influenza Pathogenesis and Control - Volume I, Current Topics in Microbiology and Immunology, 2014; 385, 377–401, doi:10.1007/82_2014_395.

[15] Cosic I: Macromolecular Bioactivity: Is it Resonant Interaction between Macromolecules? -Theory and Applications. IEEE Trans on Biomedical Engineering, 1994; 41, 1101-1114.

[16] Cosic I: Virtual spectroscopy for fun and profit. Biotechnology, 1995; 13, 236-238.

[17] Cosic I: The Resonant Recognition Model of Macromolecular Bioactivity: Theory and Applications. Basel: Birkhauser Verlag, 1997.

[18] Cosic I: Resonant Recognition Model of Protein Protein and Protein DNA Recognition in Bioinstrumentation and Biosensors. ed by Wise D. Marcel Dekker Inc., New York, 1990; 475-510.

[19] Cosic I, Cosic D: Macromolecular Resonances. In: Bandyopadhyay A., Ray K. (eds) Rhythmic Oscillations in Proteins to Human Cognition. Studies in Rhythm Engineering. Springer, Singapore, 2021; 1, 11-45, doi: 10.1007/978-981-15-7253-1_1.

[20] Cosic I, Cosic D, Lazar K: Analysis of Tumor Necrosis Factor Function Using the Resonant Recognition Model. Cell Biochemistry and Biophysics, 2015; doi: 10.1007/s12013-015-0716-3.

[21] Cosic I, Paspaliaris V, Cosic D: Analysis of Protein-Receptor on an Example of Leptin-Leptin Receptor Interaction Using the Resonant Recognition Model. MDPI Appl. Sci., 2019; 9, 5169, doi:10.3390/app9235169.

[22] Cosic I, Cosic D: DNA-Protein Interactions at Distance Explained by the Resonant Recognition Model. International Journal of Sciences, 2024; 13(11), 1-5, doi: 10.18483/ijSci.2805.

[23] Cosic I, Cosic D, Loncarevic I: Analysis of Bacteria Resistance Using the Resonant Recognition Model. International Journal of Sciences and Research Archive, 2026, 18(01), 242-251, doi: 10.30574/ijsra.2026.18.1.0050.

[24] Cosic I, Harris CM, Cosic D: CHD2 Protein Malfunction Causing Neurodevelopmental Disorders and Epilepsy as Analyzed by Resonant Recognition Model. International Journal of Sciences and Research Archive, 2025, 17(2), 574-579, doi: 10.30574/ijsra.2025.17.2.3080.

[25] Cosic I, Cosic D, Loncarevic I: New Concept of Small Molecules Interaction with Proteins – An Application to Potential COVID-19 Drugs. International Journal of Sciences, 2020; 9(9), 16-25, doi: 10.18483/ijSci.2390.

[26] Cosic I, Cosic D, Loncarevic I: Analysis of Ivermectin as Potential Inhibitor of SARS-CoV-2 Using Resonant Recognition Model. International Journal of Sciences, 2021; 10(1), 1-6, doi: 10.18483/ijSci.2433.

[27] Cosic I, Drummond AE, Underwood JR, Hearn MTW: In vitro inhibition of the actions of basic FGF by novel 16 amino acid peptides. Molecular and Cellular Biochemistry, 1994; 130, 1-9.

[28] Krsmanovic V, Biquard JM, Sikorska-Walker M, Cosic I, Desgranges C, Trabaud MA, Whitfield JF, Durkin JP, Achour A, Hearn MT: Investigation Into the Cross-reactivity of Rabbit Antibodies Raised against Nonhomologous Pairs of Synthetic Peptides Derived from HIV-1 gp120 proteins. J.Peptide Res, 1998; 52(5), 410-412.

[29] Hearn MTW, Biquard JM, Cosic I, Krsmanovic V: Peptides Immunologically related to proteins expressed by a viral agent, having a sequence of amino acids ordered by means of protein informational method. US Patent 6 294 174, 2001.

[30] Almansour N, Pirogova E, Coloe P, Cosic I, Istivan T: Investigation of cytotoxicity of negative control peptides versus bioactive peptides on skin cancer and normal cells: a comparative study. Future Medicinal Chemistry, 2012; 4(12), 1553-1565.

[31] Istivan T, Pirogova E, Gan E, Almansour N, Coloe P, Cosic I: Biological effects of a De Novo designed myxoma virus peptide analogue: Evaluation of cytotoxicity on tumor cells. Public Library of Science (PLoS) ONE, 2011; 6(9), 1-10.

[32] Cosic I, Kuhar U, Krapez U, Slavec B, Cosic D, Loncarevic I: De Novo Designed Peptide to Prevent SARS-CoV-2 Interaction with ACE2 Receptor on Host Cells. International Journal of Sciences, 2022; 11(2), 1-8, doi: 10.18483/ijSci.2558.

[33] Krapez U, Kuhar U, Šenica P, Slavec B, Cosic D, Loncarevic I, Janezic S, Cosic I: Different SARS-CoV-2 variants inhibited by RRM designed peptide. PLoS One, 2025; 20(7), doi: 10.1371/journal.pone.0327582.

[34] Cosic I, Cosic D: Peptides Inhibiting COVID-19, WO 2022/233856 A1 owned by QuantBioRes A/S. 2022, 10/112022.

[35] Mishra A, Cosic I, Loncarevic I, Cosic D, Fletcher HM: Inhibition of β-lactamase function by de novo designed peptide. PLoS ONE, 2023; 18(9), 1-15, doi: 10.1371/journal.pone.0290845.

[36] Cohen M, Zhang XQ, Senaati HP, Chen HW, Varki NM, Schooley RT, Gagneux P: Influenza A penetrates host mucus by cleaving sialic acids with neuraminidase. Virol J., 2013; 10, 321, doi: 10.1186/1743-422X-10-321.

Appendix

The Resonant Recognition Model (RRM) is innovative approach using knowledge from quantum physics, biochemistry and mathematics, which is capable to analyze interactions between proteins and their targets, which could be other proteins, DNA, RNA, or small molecules. The RRM model has been extensively previously published in detail within the number of publications [15-24]. The RRM model is based on the findings that certain periodicities (frequencies) within the distribution of energy of delocalised electrons along protein backbone are critical for macromolecule biological function and/or interaction with their targets. The distribution of delocalised electrons energies is calculated by assigning each amino acid specific physical parameter representing the energy of delocalised electrons of each residue. Consequently, the spectral characteristics of such energy distribution (signal) are calculated using Fourier Transform. This means that the linear numerical signal representing the distribution of energies along the macromolecule is transformed into the frequency domain and is characterised by number of different frequencies containing all information from the original signal. Comparing such spectra using cross-spectral function for macromolecules, which are sharing the same biological function/interaction, it has been shown that they share the same frequency within the spectrum of free energy distribution along the macromolecule [15-24]. Peak frequencies in such multiple cross-spectral function present common frequency components for all macromolecular sequences compared. The comprehensive analysis done so far confirms that all macromolecular sequences, with the common biological function and/or interaction, have common frequency components, which are specific features for the observed biological function/interaction [15-24]. Thus, each specific macromolecular biological function/interaction within macromolecule is characterised by specific RRM frequency.

Generally, biological functions are driven by proteins that selectively interact with other proteins, DNA/RNA regulatory segments or small molecules. Through extensive use of RRM model, it has been shown that proteins and their targets share the same matching RRM characteristic frequency [15-24]. The matching of periodicities within the distribution of energies of free electrons along the interacting proteins can be regarded as the resonant recognition and as such is highly selective. Thus, RRM frequencies characterise not only protein function, but also recognition and interaction between protein and its targets: proteins (receptors, binding proteins, and inhibitors), DNA/RNA regulatory segments or small molecules. In addition, it has been also shown that interacting macromolecules have opposite phases at their characteristic RRM recognition frequency [15-24].

Once the characteristic frequency for biological function and/or interaction of the macromolecule is identified, it is possible to design new peptides/proteins with the desired RRM frequency components [15-17] and consequently have been experimentally tested to have indeed desired biological functions and/or interactions [27-35].

As it has been proposed that the RRM frequencies characterise, not only a general function, but also a recognition and interaction between the macromolecule and its target, it could be considered as resonant recognition. This resonance could be achieved with resonant energy transfer between the interacting macromolecules through oscillations of a physical field, which could be electromagnetic in nature. Since there is evidence that proteins and DNA have certain conducting properties, a charge moving through the macromolecular backbone and passing different energy stages, caused by different amino acid or nucleotide side groups, can produce sufficient conditions for a specific electromagnetic radiation or absorption. The frequency ranges of this field depend on the charge velocity. The RRM model proposes that the charge is traveling through the macromolecular backbone at the estimated velocity of $7.87x10^5$m/s [15-26]. For this velocity and with the distance between amino acids in a protein molecule of 3.8Å, the frequency of protein interactions was estimated to be in the range between 10^{13}Hz and 10^{15}Hz. Therefore, the estimated frequency range for both amino acid and nucleotide macromolecules include far infra-red, infra-red, visible and part of ultra-violet light. To support this idea, we compared our computational predictions with number of published experimental results [15-24]. These comparisons have shown a strong linear correlation between frequencies, as calculated using the RRM model and experimentally measured characteristic frequencies, with the slope factor of K=201 [15-26]. This frequency range is overlapping the frequency range previously associated with the RRM numerical frequency spectrum that has been calculated from the charge velocities through the protein backbone [15-24]. This correlation can be presented as follows:

$$\lambda = K / f_{rrm}$$

where λ is the wavelength of light irradiation in nm, which can influence particular biological process, f_{rrm} is RRM numerical frequency and K is coefficient of this linear correlation.

The initially established RRM approach cannot be applied for interactions between proteins and small molecules, as small molecules are not linear sequential molecules. To be able to analyse interaction between small molecules and proteins, we have proposed that small molecules also recognise proteins on the distance and interact with proteins through electromagnetic resonant energy transfer enabling specific biological activity [25-26]. To expand the idea of electromagnetic resonant recognition to small molecules and their interaction with proteins, RRM model has been extended by calculating electromagnetic frequencies of free electron energies within the small molecule and comparing these frequencies with RRM characteristic frequencies for relevant interacting proteins [25-26].

The RRM resonant frequency of small molecules can be calculated as follows [25-26]:

$$f_{sm} = (K \times E) / (h \times (c / n))$$

where: f_{sm} is numerical RRM frequency corresponding to electromagnetic radiation resonances due to energies of free electrons within small molecules, K=201 is coefficient in nm previously semi empirically identified to characterise the relationship between RRM frequencies and related electromagnetic radiation frequencies, E is energy of free electrons within small molecules, h is Planck constant, c is speed of light, n is refraction index in biological materials.

The hypothesis that frequencies produced by energies of free electrons within small molecules are critical for small molecules' biological functions and their recognition and interaction with proteins, has been tested for a number of small molecules interacting with their receptors [25-26].