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Analysis of Myelin using the Resonant Recognition Model

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Abstract: Both Multiple Sclerosis (MS) and possibly Alzheimer Disease (AD) are caused by damage of myelin sheath, which is an insulating layer of lipids and proteins surrounding nerves. By using the Resonant Recognition Model (RRM), which can identify critical parameters for function/interaction of biological molecules, we have analysed here all the participants in the formation and stability of myelin with the aim to understand its complex function. Interestingly, we have identified here that all participants in myelin formation and stability do have only one common RRM frequency, indicating that this RRM frequency is critical for myelin formation and stability. With such identified RRM characteristic frequency, the next step would be to design *de novo* bioactive peptides, which might be able to facilitate repair of damaged myelin and could lead to new possible treatment of MS and AD.

Keywords: Myelin, Multiple Sclerosis, Alzheimer Disease, Resonant Recognition Model

Introduction

Diseases, like Multiple Sclerosis (MS) and Alzheimer Disease (AD), do have serious consequences to people's life and are becoming more prevalent with ageing population. Both MS and AD are not well understood and do not have any specific cure, but it seems that both diseases have a similar source, i.e. damage of myelin sheath. Myelin is an insulating layer of lipids and proteins surrounding nerves and if damaged can cause problems with the nerves' ability to send and receive electrical messages which can lead to MS and possibly AD.

Multiple sclerosis (MS) is a disease in which the insulating covers of nerve cells in the brain and spinal cord becomes damaged. Such damage disrupts the ability of certain parts of the nervous system to transmit signals resulting in the main characteristics of MS, which causes the formation of lesions in the central nervous system, inflammation, and the destruction of myelin sheaths of neurones. These features interact in a complex and in a not yet fully understood manner that produces the breakdown of nerve tissue, and in turn, the signs, and symptoms of the MD disease [1]. In addition, there is accumulating evidence that myelin impairment is an important part of the pathological changes observed in Alzheimer Disease (AD), but is still difficult to say whether myelin damage itself is sufficient to drive the neurodegenerative process and the cognitive decline in AD. Although AD pathology is used to be typically linked with neuronal degeneration, most recent data demonstrates that AD is strongly associated with pathology of myelin [2]. This data is supported by human MRI neuroimaging studies, but also by biochemical and postmortem studies. Thus, recent findings suggest that myelin probably plays a more important role in AD pathology than previously thought [2].

To understand the myelin function and the process of demyelination in different diseases including Multiple Sclerosis, Alzheimer Disease, and others, it is important to understand myelin content and functions of particular constituents and regulators. Most nerve fibres inside and outside the brain are wrapped with many layers of tissue composed of a fat (lipoprotein) called myelin. These layers form the myelin sheath, much like the insulation around an electrical wire, enables nerve signals (electrical impulses) to be conducted along nerve fibres with speed and accuracy. When this sheath is damaged, the nerves do not conduct electrical impulses normally and sometimes the nerve fibres are also damaged [3-7].

Myelin is a lipid-rich material that surrounds nerve cell axons to insulate them and increase the rate at which electrical impulses are passed along the axon [3]. The loss of myelin, as mentioned above, causes

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a number of diseases, including the most prominent, Multiple Sclerosis (MS) and possibly Alzheimer Disease (AD). The protein content of myelin includes myelin basic protein (MBP) [4], which is abundant in the central nerve system (CNS), where it plays a critical, non-redundant role in formation of compact myelin; myelin oligodendrocyte glycoprotein (MOG) [5], which is specific to the CNS; and proteolipid protein (PLP) [6], which is the most abundant protein in CNS myelin, but only a minor component of periphery nerve system (PNS) myelin. In the PNS, myelin protein zero (MPZ or P0) has a similar role to that of PLP in the CNS, as it is involved in holding together the multiple concentric layers of glial cell membrane that constitute the myelin sheath. Cholesterol is an essential lipid component of myelin, without which myelin fails to form [7].

With the aim to understand the complex function of myelin, we have utilised the Resonant Recognition Model (RRM) to analyse all proteins included in myelin, as well as cholesterol as small molecule, which is an essential lipid component of myelin. The better understanding of the complex functionality of myelin is the first step towards finding the possible treatment for myelin related diseases.

Methods

Resonant Recognition Model

The Resonant Recognition Model (RRM) is a biophysical, theoretical model that can analyse interactions between proteins and their targets, which could include proteins, DNA, RNA, or small molecules. The RRM has been previously published in detail within number of publications [8-14]. 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. In other words, each specific macromolecular biological function/interaction within macromolecule is characterised by a specific RRM frequency. Furthermore, through extensive use of RRM model, it has been shown that proteins and their targets share the same matching RRM characteristic frequency within the distribution of energies of free electrons along the interacting proteins, which can be regarded as the resonant recognition and as such is highly selective [8-14].

Once the characteristic frequency for biological function and/or interaction of the macromolecule is identified, it is possible to design *de novo* peptides/proteins with the desired RRM frequency components and consequently with desired biological functions and/or interactions [8-11,15-24]. This concept of *de novo* designed bioactive peptides using the RRM model has already been successfully applied and experimentally tested in a number of examples in the design of: peptide that can prevent resistant bacteria [24], peptide that can prevent SARS-CoV-2 virus entry into the host cells via ACE2 receptor [22-23], peptide to mimic myxoma virus oncolytic function [21], IL-12 analogue [20], peptides related to skin cancer [19], HIV envelope protein analogue [16-18], FGF analogue [15].

As it has been proposed previously, the RRM frequencies characterise resonant recognition and interaction between the protein and its target, and this could be achieved with resonant energy transfer between the interacting biological molecules. The RRM model proposes that this resonant energy transfer is electromagnetic in nature within the frequency range between 10^{13}Hz and 10^{15}Hz, which includes far infra-red, infra-red, visible, and some ultra-violet light. This has been experimentally tested in number of examples including electromagnetic frequencies activating l-lactate dehydrogenase [25], photon emission from dying melanoma cells [26], photon emission from lethal and non-lethal Ebola strains [27], JAK-STAT signalling pathway [28], osteoblastic differentiation of stem cells by photo bio-modulation [29] and the use of external blue light in treatment of Crigler–Najjar syndrome [30]. These calculations and experiments have shown a strong linear correlation between frequencies calculated by the RRM and the experimentally measured characteristic frequencies, with the slope factor of K=201 [8-11]:

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

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

The initially established RRM approach [8-14] cannot be applied for interactions between proteins and small molecules, as small molecules are not linear sequential molecules. 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 [31-32].

The RRM resonant frequency of small molecules can be calculated as follows [31-32]:

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

where: f_{sm} is RRM frequency corresponding to electromagnetic radiation resonances due to energies of free electrons within small molecules, K=201 is coefficient 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 [31-32].

Here, we have applied the RRM model, as explained above, to analyse all proteins contained within myelin and cholesterol as a small molecule, which is an essential lipid component of myelin.

Results

Firstly, we have analysed here, using the RRM model, the proteins that are contained in myelin. Although, there is a number of different proteins contained in myelin, and even they are found in different nerve systems (CNS and PNS) they all have a similar function in formation of myelin and holding together the myelin sheath. The proteins that we have analysed are from the UniProt database as follows: myelin basic protein MBP (P02686, P02687, P02688, P04370, P15720, P25274, P81558, P83487, P06906, P25188, P87346, Q91325, Q91439, P20939, P98190), myelin oligodendrocyte glycoprotein MOG (Q9BGS7, Q5R960, Q29ZQ1, P55803, Q63345, Q61885, Q16653), proteolipid protein PLP (Q712P7, P47790, P47789, P23289, P23294, P60203, P60202, P60201, P04116) and myelin protein zero MPZ (P37301, P20938, A2VD98, A0JM41, Q6WEB5, P27573, P25189, P10522, P06907). As these proteins have a similar and critical role in formation and stability of myelin, we expect that they would have the common RRM frequency related to myelin's critical biological function. When we have compared all these proteins, we have indeed found that they have only one common RRM frequency at f=0.1953±0.0060, as presented in Figure 1. According to RRM principles, such common RRM frequency is related to common biological function of analysed proteins, i.e. formation and stability of myelin.

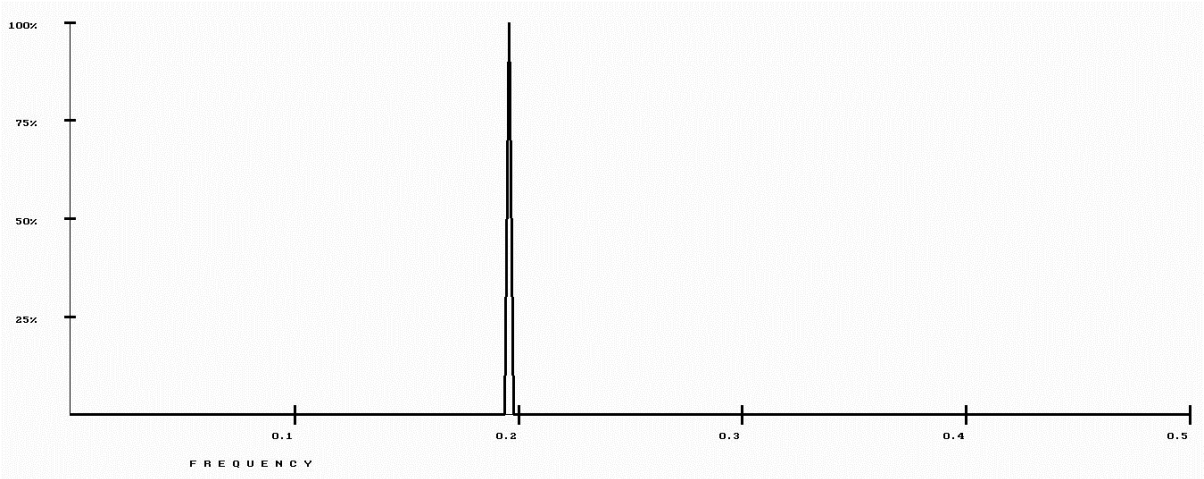

Figure 1. RRM characteristic frequency f=0.1953±0.0060 common for all proteins contained in myelin.

As cholesterol is an essential lipid component of myelin, we have analysed using the RRM model, the relationship between cholesterol as a small molecule and proteins within myelin responsible for myelin formation and stability. For that purpose, we have used RRM calculation for small molecules as presented in the formula above and is detailed in references [31-32]. Using the chemical formula for cholesterol $C_{27}H_{46}O$, we have calculated the energy of free electrons within cholesterol to be at E=0.0605Ry. For this energy and refraction index for proteins between 1.36-1.55, we have calculated the corresponding RRM frequency for cholesterol to be in between 0.18-0.21, as highlighted in yellow in Figure 2.

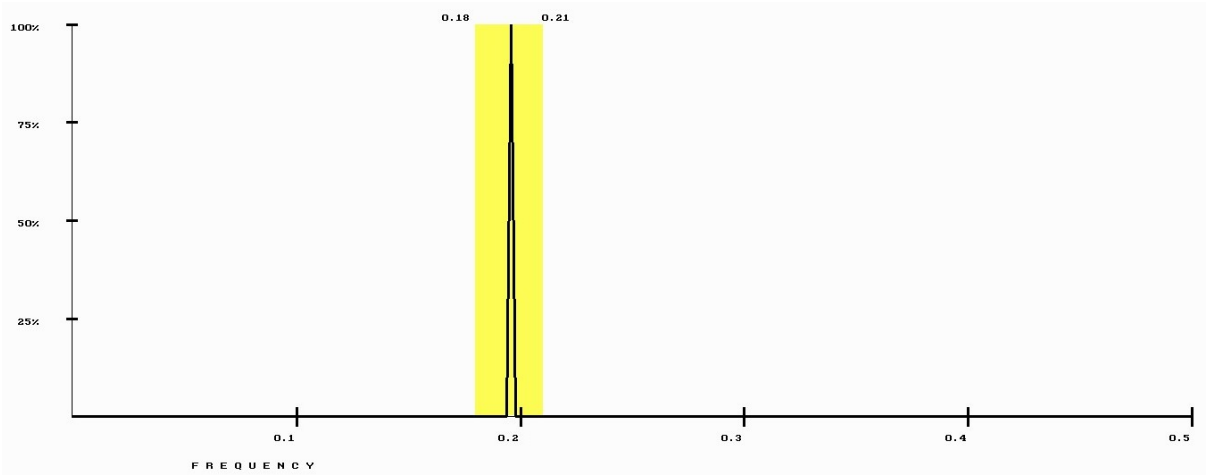

Figure 2. RRM characteristic frequency f=0.1953±0.0060 common for all proteins contained in myelin overlapping with cholesterol RRM frequency range between 0.18-0.21 highlighted in yellow.

It is important to notice that the RRM frequency range of 0.18-0.21 for cholesterol overlaps characteristic RRM frequency for proteins responsible for myelin formation and stability of f=0.1953±0.0060. The fact that those two frequency ranges are overlapping is confirmation that the RRM model can recognise complex relationships between proteins involved in myelin formation and stability, as well as cholesterol as main content of myelin. Even more the RRM model describes this complex relationship through single number representing resonant frequency for all constituents in the process of myelin existence. Once when such characteristic frequency has been identified, we can use it to design *de novo* peptides, as we did successfully in number of other examples [15-24], that would be able to repair damaged myelin, which possibly could be used for treatment of MS and AD.

Discussion

Both Multiple Sclerosis (MS) and possibly Alzheimer Disease (AD) are caused by damage of myelin sheath, which is an insulating layer of lipids and proteins surrounding the nerves [1-7]. To better understand the cause of these diseases and possibly lead to the treatment, we have here analysed all the participants in the formation and stability of myelin. For that purpose, we have used the Resonant Recognition Model (RRM), which can identify critical parameters for function/interaction of biological molecules. Interestingly, we have identified that all participants in the myelin formation and stability, both proteins and cholesterol as small molecule, do have only one common RRM frequency at f=0.1953±0.0060, indicating that this frequency is critical for myelin formation and stability. With such identified RRM characteristic frequency, the next step would be to design *de novo* bioactive peptides using already established and successfully tested RRM procedure [15-24]. Such designed peptides might be able to facilitate repair of damaged myelin and could lead to new possible treatment of MS and AD.

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References

1. Compston A, Coles A (October 2008). "Multiple sclerosis". Lancet. 372 (9648): 1502–1517. doi:10.1016/S0140-6736(08)61620-7.
2. Papuć E, Rejdak K. The role of myelin damage in Alzheimer's disease pathology. Arch Med Sci. 2018 Aug 28;16(2):345-351. doi: 10.5114/aoms.2018.76863.
3. Bean, Bruce P. (June 2007). "The action potential in mammalian central neurons". Nature Reviews Neuroscience, 8 (6): 451–465, doi:10.1038/nrn2148.
4. Steinman L: Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. Cell, 1996; 85(3), 299–302, doi: 10.1016/S0092-8674(00)81107-1.
5. Mallucci G, Peruzzotti-Jametti L, Bernstock JD, Pluchino S: The role of immune cells, glia and neurons in white and gray matter pathology in multiple sclerosis. Progress in Neurobiology, 2015; 127–128, 1–22, doi: 10.1016/j.pneurobio.2015.02.003.
6. Greer JM, Lees MB: Myelin proteolipid protein--the first 50 years. The International Journal of Biochemistry & Cell Biology, 2002; 34(3), 211–215, doi: 10.1016/S1357-2725(01)00136-4.
7. Saher G, Brügger B, Lappe-Siefke C, Möbius W, Tozawa R, Wehr MC, Wieland F, Ishibashi S, Nave KA: High cholesterol level is essential for myelin membrane growth. Nature Neuroscience, 2005; 8(4), 468–470, doi: 10.1038/nn1426.
8. Cosic I: Macromolecular Bioactivity: Is it Resonant Interaction between Macromolecules? -Theory and

Applications. IEEE Trans on Biomedical Engineering, 1994; 41, 1101-1114.
9. Cosic I: Virtual spectroscopy for fun and profit. Biotechnology, 1995; 13, 236-238.
10. Cosic I: The Resonant Recognition Model of Macromolecular Bioactivity: Theory and Applications. Basel: Birkhauser Verlag, 1997.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. Achour A, Biquard JM, Krsmanovic V, M'Bika JP, Ficheux D, Sikorska M, Cozzone AJ: Induction of Human Immunodeficiency Virus (HIV-1) Envelope Specific Cell-Mediated Immunity by a Non-Homologus Synthetic Peptide. PLoS ONE, 2007; 11, 1-12, doi: 10.1371/journal.pone.0001214.
19. 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.
20. Pirogova E, Istivan T, Gan E, Cosic I: Advances in Methods for Therapeutic Peptide Discovery, Design and Development. Current Pharmaceutical Biotechnology, 2011; 12, 1117-1127.
21. 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.
22. 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.
23. Cosic I, Cosic D: Peptides Inhibiting COVID-19. WO 2022/233856 A1 owned by QuantBioRes A/S. 2022, 10/112022.
24. 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.
25. Vojisavljevic V, Pirogova E, Cosic I: The Effect of Electromagnetic Radiation (550nm-850nm) on I-Lactate Dehydrogenase Kinetics. Internat J Radiat Biol, 2007; 83, 221-230.
26. Dotta BT, Murugan NJ, Karbowski LM, Lafrenie RM, Persinger MA: Shifting Wavelength of Ultraweak Photon Emissions from Dying Melanoma Cells: Their Chemical Enhancement and Blocking Are Predicted by Cosic's Theory of Resonant Recognition Model for Macromolecules. Naturwissenschaften, 2014; 101(2), doi: 10.1007/s00114-013-1133-3.
27. Murugan NJ, Karbowski LM, Persinger MA: Cosic's Resonance Recognition Model for Protein Sequences and Photon Emission Differentiates Lethal and Non-Lethal Ebola Strains: Implications for Treatment. Open Journal of Biophysics, 2014; 5, 35.
28. Karbowski LM, Murugan NJ, Persinger MA: Novel Cosic Resonance (Standing Wave) Solutions for Components of the JAK-STAT Cellular Signalling Pathway: A Convergence of Spectral Density Profiles. FEBS Open Bio, 2015; 5, 245-250.
29. Cosic I, Paspaliaris V, Cosic D: Explanation of Osteoblastic Differentiation of Stem Cells by Photo Biomodulation Using the Resonant Recognition Model. Appl. Sci., 2019; 9, 1979, doi: 10.3390/app9101979.
30. Cosic I, Cosic D: The Treatment of Crigler-Najjar Syndrome by Blue Light as Explained by Resonant Recognition Model. EPJ Nonlinear Biomedical Physics, 2016; 4(9), doi: 10.1140/epjnbp/s40366-016-0036-6.
31. 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.
32. 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.