International Journal of Sciences

Research Article Volume 13 – November 2024 (11)

DNA-Protein Interactions at Distance Explained by the Resonant Recognition Model

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Abstract: It is very hard to accept that fast, precise and efficient biomolecular interactions within living cells in an environment heavily populated with other molecules which is happening only by random movement of molecules. A more realistic approach would be to have long distance recognition that will guide interacting molecules towards each other. With this idea in mind, it has been recently experimentally measured that the recognition between interacting biomolecules occurs on a distance through resonant electrodynamic intermolecular forces. To theoretically explain such measurements, we have employed the Resonant Recognition Model (RRM), which is the unique model predicting that biomolecular interactions are based on resonant electromagnetic energy transfer for distant recognition and interaction between interacting molecules. Here, we have applied the RRM model to analyse the interaction between EcoRI enzyme and double helix DNA primer containing EcoRI cleavage site. We have identified the characteristic frequency for this interaction, proposing that resonant electromagnetic energy is responsible for enzyme and DNA long distance recognition.

Keywords: Biomolecular long distance recognition, EcoRI enzyme, Resonant Recognition Model

Introduction

The life is underlined by dynamic biomolecular interactions within a complex network of biomolecules including proteins, nucleic acids and small molecules. Although there is an enormous number of interactions among those biomolecules at any time, these interactions are performing with tremendous precision and efficiency. The forces that are driving those interactions are still not fully understood. Currently it is proposed that these interactions are based on chemical and hydrogen bonds, as well as Coulomb and van der Waals forces, which are relevant at short distances only. To understand how the right molecule gets to the right place at the right moment in the right cascade of biological events is still a big challenge and is currently the matter of recent scientific explorations and experiments [1-6]. To fully explain speed, precision and efficiency of biomolecular interactions there is a need for a theory that can incorporate forces that propagate through resonance with minimal loss of energy within biological materials including water. One of such theories is the Resonant Recognition Model (RRM), which is the unique model predicting that biomolecular interactions are based on resonant electromagnetic energy transfer for distant recognition and interaction between interacting biomolecules [7-18]. Such possibility can explain enabling long distance molecular interactions, which can then explain discrepancy between the currently accepted "lock-and-key" model and actual velocity and precision of biomolecular interactions. This present paper has been motivated by a number of theoretical and experimental findings within references [1-6], where the possibility of long distance electrodynamic intermolecular forces has been discussed and experimentally tested. Moreover, it has been experimentally demonstrated that there is 'activation of resonant electrodynamic intermolecular forces' with 'experimental proof of principle of a physical phenomenon that have been observed for biomolecules and within long range action (up to 1000Å) could be importance for biology' [4]. Here, we have addressed selective electrodynamic interactions between DNA and protein using the RRM model. For that purpose, we have analysed the interaction between EcoRI restriction enzyme that cleaves DNA double helices into fragments at specific cleavage site: GAATTC. Although this site is well known, the question is how the enzyme can recognise this specific site on distance precisely and efficiently within double stranded DNA environment. Our RRM analysis is based on example presented if reference [5].

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 be other proteins, DNA, RNA, or small molecules. The RRM has been previously published in detail within a number of publications [7-18]. The RRM model is based on the findings that certain periodicities (frequencies) within the distribution of energy of delocalized electrons along protein backbone are critical for protein biological function and/or interaction with their targets. The distribution of the delocalised electrons energies is calculated by assigning each amino acid specific physical parameter representing the energy of delocalised electrons of each amino acid [7-8]. Consequently, the

Published at: http://www.ijsciences.com/pub/issue/2024-11/
DOI: 10.18483/ijSci.2805; Online ISSN: 2305-3925; Print ISSN: 2410-4477

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spectral characteristics of such energy distribution (signal) are calculated using Fourier Transform. It has been shown that proteins with similar biological function and interaction have a common frequency component in such spectrum and that this frequency component is characterising observed biological function and interaction. In addition, it has also been shown that interacting macromolecules have opposite phases at their characteristic RRM recognition frequency [7-18].

Knowing the characteristic frequency of a particular protein function, creates the possibility to predict which amino acids or nucleotides prevail in the sequence and predominantly contribute to this frequency and consequently to the observed function using the inverse procedure. These sensitive amino acids or nucleotides ("hot spots") are related to characteristic frequency and consequently to the corresponding biological function. Such “hot spots” have been predicted and compared with experimental results in a number of protein and DNA examples including interleukin-2 [7], SV40 enhancer [19], Epidermal Growth factor EGF [7], Ha-ras p21 oncogene product [7], glucagons [7], haemoglobins [20-21], myoglobins[20-21], lysozymes[20-21], Tumour Necrosis factor TNF [9] and BRCA1/BRCA2 [22].

The RRM model is a unique approach, where it is possible to analyse interactions directly computationally between amino acid sequences (proteins) and nucleotide sequences (DNA and RNA), based only on matching frequencies within free electron energy distribution along these macromolecules. However, for the comparison of characteristic frequencies between proteins and DNA/RNA macromolecules, it is required to adjust for the difference in distances between amino acids (3.8Å) and nucleotides (3.4Å) along the macromolecular backbone. These adjustments are made on the nucleotide sequences spectrum, so the result could be compared with frequency calculations made for the proteins. These calculations enable the RRM to be the unique model capable of analysing and directly comparing activities and interactions of proteins, DNA and RNA by identifying their characteristic frequencies, as tested, and described in number of previous publications [7-8,12,14,23].

The RRM frequencies characterise recognition and interaction between the macromolecule and its target, which could be achieved with resonant energy transfer between the interacting macromolecules through oscillations of a physical field, possibly electromagnetic in nature. Since there is evidence that proteins and DNA have certain conducting or semi-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 proposes that the charge is travelling through the macromolecular backbone at the estimated velocity of 7.87×10^5m/s [7-8,13-18]. 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, encompassing far infra-red, infra-red, visible, and ultra-violet light.

The strong linear correlation between RRM calculated frequencies and experimentally measured characteristic frequencies, have been established with the slope factor of K=201 [7-8,15-18]. This correlation can be represented as following:

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

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.

We applied this concept on number of proteins and DNA examples [7-8,13-18]. The concept has been also experimentally tested on activation of L-Lactate Dehydrogenase [18], on photon emission from dying melanoma cells [24], on photon emission from lethal and non-lethal Ebola strains [25], as well as on classic signalling pathway, JAK-STAT, traditionally composed of nine sequential protein interactions [26]. Even more, the RRM for the first time explains how and why external blue light can be used in the treatment of Crigler-Najjar syndrome [16]. These findings could be used, not only to understand biological processes and resonances in biomolecules, but also to influence these processes using either radiation or design of related molecules and conductive particles.

The fact that RRM model has shown that biomolecular recognitions and interactions are based on resonant electromagnetic energy, can explain experimental evidence for long distance electrodynamic intermolecular forces, crucial for biomolecular activity.

Results

Here, we have addressed selective electromagnetic interactions between DNA and protein by applying the RRM model to interaction between EcoRI restriction enzyme and DNA double helix. EcoRI is a restriction endonuclease enzyme that cleaves DNA double helices at very specific site as presented in red within Figure 1. Although EcoRI cleavage site (GAATTC) is very specific within the long double helix DNA, it is a puzzle how quickly and precisely

the EcoRI restriction enzyme can find this cleavage site. The theory which has been already experimentally tested is that EcoRI enzyme can recognise cleavage site resonantly on a distance and requires surrounding DNA sequence as the primer [1-6].

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5'- ATGGCTAATGACCGAGAATAGGGATCCGAATTCAATATTGGTACCTACGGGCTTTGCGCTCGTATC -3'
3'- TACCGATTACTGGCTCTTATCCCTAGGCTTAAGTTATAACCATGGATGCCCGAAACGCGAGCATAG -5'
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Figure 1. 66bp DNA sequence and cleavage site on the sequence in red.

We have applied here the RRM model to analyse forces driving DNA-enzyme interaction between 66bp oligonucleotide containing a cleavage of the EcoRI enzyme and EcoRI enzyme itself, as presented in Figure 2.

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SNKKQSNRLTEQHKLSQGVIGIFGDYAKAHDLAVGEVSKLVKKALSNEYPQLS
FRYRDSIKKTEINEALKKIDPDLGGTLFVSNSSIKPDGGIVEVKDDYGEWRVV
LVAEAKHQGKDIINIRNGLLVGKRGDQDLMAAGNAIERSHKNISEIANFMLSE
SHFPYVLFLEGSNFLTENISITRPDGRVVNLEYNSGILNRLDRLTAANYGMPI
NSNLCINKFVNHKDKSIMLQAASIYTQGDGREWDSKIMFEIMFDISTTSLRVL
GRDLFEQLTSK
```

Figure 2. EcoRI enzyme – amino acid sequence (276 residues from UniProt database: P00642).

The RRM model is a unique approach, where it is possible to analyse interactions directly computationally between amino acid sequences (proteins) and nucleotide sequences (DNA and RNA), based only on matching frequencies within free electron energy distribution along these macromolecules. When we have applied the RRM model to compare 66bp oligonucleotide containing a cleavage of the EcoRI enzyme and EcoRI enzyme, we have found a very strong common RRM frequency at f=0.1699±0.0152, indicating that this frequency is crucial for mutual recognition and interaction between 66bp oligonucleotide and EcoRI enzyme, as presented in Figure 3.

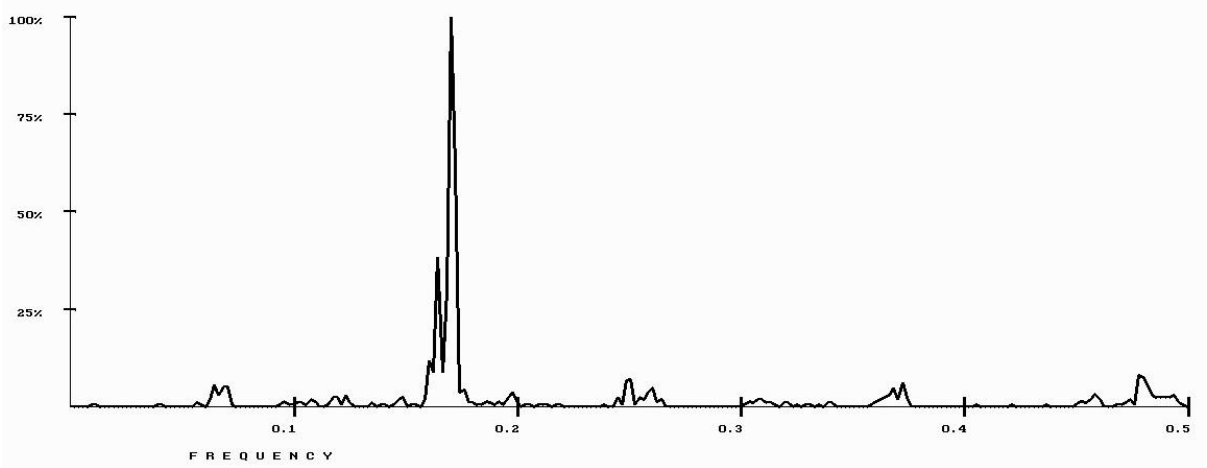

Figure 3. Characteristic RRM frequency for mutual interaction between 66bp oligonucleotide and EcoRI enzyme at f=0.1699±0.0152.

When we have applied the RRM "hot spot" analysis, as explained in Methods, we have identified that nucleotide pair C-G at the position 33 is mostly contributing to RRM characteristic frequency at f=0.1699±0.0152 and thus represent "hot spot" for this interaction. It is important to notice that pair C-G at the position 33 is within the cleavage site of 66bp oligonucleotide, which is the centre point of this interaction.

It was found here that the RRM frequency at f=0.1699±0.0152 characterise recognition on distance and interaction between EcoRI restriction enzyme and DNA double helix. This recognition and interaction are proposed to be achieved through resonant electromagnetic energy transfer on distance between interacting macromolecules. This electromagnetic frequency depends on velocity of charge transfer through macromolecular backbone. For the charge velocity of 7.87×10^5m/s as proposed by the RRM [7-18], the corresponding electromagnetic frequency for RRM frequency at f=0.1699±0.0152 would be from 160THz to 192THz. According to RRM principles, which have been also experimentally tested [15-18, 24-26], this frequency range is significant for biological recognition on the

distance between EcoRI restriction enzyme and DNA double helix, which contains specific cleavage site GAATTC, as well as for activation of cleavage process of EcoRI restriction enzyme on DNA double helix. In addition, there is a possibility of other vibrations in biological macromolecules, which possibly are not biologically related and will depend on other possible charge velocities within macromolecules [13]. For example, for the velocity of $1.2x10^5$m/s as proposed by Yomosa, the corresponding electromagnetic frequency for RRM frequency at f=0.1699±0.0152 would be from 24THz to 29THz [13].

Discussion

Currently proposed theories (like "lock-and-key" model) of biomolecular interactions are based on forces that are effective at short distances only. However, such theories cannot fully explain the speed, precision and efficiency of biomolecular interactions, thus there is a need for a theory that can incorporate forces that propagate with minimal loss of energy within biological materials including water. One of such forces could be based on resonant electromagnetic energy transfer, which can transfer energy on the long distance. This concept can be used for the analysis of macromolecular recognition on the long distance, as proposed by the Resonant Recognition Model (RRM). Here, we have applied the RRM model on recognition and interaction between EcoRI restriction enzyme and double helix DNA primer containing EcoRI cleavage site. Interestingly, we have found only one prominent common RRM frequency at f=0.1699±0.0152, that corresponds to electromagnetic frequency range of 160THz to 192THz, between enzyme and DNA characterising their recognition on distance and interaction. According to RRM principles, which have also been experimentally tested [15-18, 24-26], this frequency range is significant for biological recognition on distance between EcoRI restriction enzyme and DNA double helix, which contains specific cleavage site GAATTC, as well as for activation of cleavage process of EcoRI restriction enzyme on DNA double helix. This paper represents the possible theoretical explanation of experimental results [5], showing that there is a long distance recognition between EcoRI restriction enzyme and double helix DNA primer containing EcoRI cleavage site. Generally, the same approach can be applied for any long distance recognition and interaction between biomolecules within living systems.

Author Contributions: I.C. and D.C. equally contributed to all aspects of this paper.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Acknowledgement: We want to thank prof Marco Pettini for constructive discussions and miss Amy Cosic for proofreading of this paper.

References

1. Preto J, Pettini M, Tuszynski J: On the role of electrodynamic interactions in long-distance biomolecular recognition. Phys. Rev., 2015; E91, 052710, doi: 10.1103/PhisREvi.91.052710.
2. Nardecchia I, Lechelon M, Gori M, Donato I, Floriani E, Jaeger S, Mailfert S, Marguet D, Ferrier P, Pettini M: Detection of long-distance electrostatic interactions between biomolecules by means of Fluorescence Correlation Spectroscopy. Phys. Rev., 2017; E96, 022403, doi: 10.1103/PhisREvi.96.022403.
3. Nardecchia I, Spinelli L, Preto J, Gori M, Floriani E, Jaeger S, Ferrier P, Pettini M: Experimental detection of long-distance interactions between biomolecules through their diffusion behavior: Numerical study. Phys. Rev., 2014; E90, 022703, doi: 10.1103/PhisREvi.90.022703.
4. Lechelon M, Meriguet Y, Gori M, Nardecchia I, Floriani E, Ruffenach S, Coquillat D, Teppe F, Mailfert S, Marguet D, Ferrier P, Varani L, Sturgis J, Torres J, Pettini M: Experimental evidence for long-distance electrodynamic intermolecular forces. Sci. Adv., 2022; 8, eabl5855, doi: 10.1126/sciadv.abl5855.
5. Kettlin U, Koltermann A, Schwille P, Eigen M: Real-time enzyme kinetics monitored by dual-color fluorescence cross-correlation spectroscopy. Proc. Natl. Acad. Sci., 1998; USA 95, 1416, doi: 10.1073/pnas.95.4.1416.
6. Kurian P, Capolupo A, Craddock TJA, Vitiello G: Water-Mediated Correlations in DNA-Enzyme Interactions. Physics Letters, 2018; A382, 33, doi: 10.1016/j.physleta.2017.10.038.
7. Cosic I: Macromolecular Bioactivity: Is it Resonant Interaction between Macromolecules? -Theory and Applications. IEEE Trans on Biomedical Engineering, 1994; 41, 1101-1114.
8. Cosic I: The Resonant Recognition Model of Macromolecular Bioactivity: Theory and Applications. Basel: Birkhauser Verlag, 1997.
9. 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.
10. Cosic I, Paspaliaris V, Cosic D: Analysis of Protein-Receptor on an Example of Leptin-Leptin Receptor Interaction Using the Resonant Recognition Model. Appl. Sci., 2019; 9,5169 doi: 10.3390/app9235169.
11. 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.
12. Cosic I, Lazar K, Cosic D: Cellular Ageing - Telomere, Telomerase and Progerin analysed using Resonant Recognition Model. MD-Medical Data, 2014; 6(3), 205-209.
13. Cosic I, Lazar K, Cosic D: Prediction of Tubulin resonant frequencies using the Resonant Recognition Model (RRM). IEEE Trans. on NanoBioscience, 2015; 12, 491-496, doi: 10.1109/TNB.2014.2365851.
14. Cosic I, Cosic D, Lazar K: Is it possible to predict electromagnetic resonances in proteins, DNA and RNA?. Nonlinear Biomedical Physics, 2015; 3, doi: 10.1140/s40366-015-0020-6.
15. Cosic I, Cosic D, Lazar K: Environmental Light and Its Relationship with Electromagnetic Resonances of Biomolecular Interactions, as Predicted by the Resonant Recognition Model. International Journal of Environmental

Research and Public Health, 2016; 13(7), 647, doi: 10.3390/ijeprh13070647.
16. 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.
17. 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: 0.3390/app9101979.
18. 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.
19. Cosic I, Nesic D: Prediction of "Hot Spots" in SV40 Enhancer and Relation with Experimental Data. Eur. J. Biochem., 1988; 170, 247-252.
20. Cosic I, Hodder AN, Aguilar MI, Hearn MTW: Resonant Recognition Model and Protein Topography: Model Studies with Myoglobin, Hemoglobin and Lysozyme. Eur. J. Biochem, 1991; 198, 113-119.
21. Cosic I, Hearn MTW: "Hot Spot" Amino Acid Distribution in Ha-ras Oncogene Product p21: Relationship to Guanine Binding Site. J. Molecular Recognition, 1991; 4, 57-62.
22. Cosic I, Cosic D, Lazar K: Cancer Related BRCA-1 and BRCA-2 Mutations as Analysed by the Resonant Recognition Model, Journal of Advances in Molecular Biology. 2017; 1(2), doi: 10.22606/jamb.2017.12003.
23. Cosic I, Hearn MTW: Studies on Protein-DNA Interactions Using the Resonant Recognition Model: Application to Repressors and Transforming Proteins. Eur. J. Biochem, 1992; 205, 613-619.
24. 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.
25. 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.
26. 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.