Studies in Rhythm Engineering

Anirban Bandyopadhyay
Kanad Ray
Editors

Rhythmic Oscillations in Proteins to Human Cognition

Springer

Studies in Rhythm Engineering

Series Editors

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Preface

On the eve of our first book in the series of Studies in Rhythm Engineering, SRE by Springer Nature, we would like to convey the readers that we are open to all topics, wherever, periodic events are there. Our objective is to explore and document fundamental research carried out globally from astrophysics to particle physics, from stock market to economic theories, and from plant biology to consciousness—we do not want to leave any stone unturned. In many years to come, the book series would answer a fundamental query to this universe, "Are all events in the universe, periodic, random and linear events are illusion, due to poor understanding of the phenomena?"

The current book emphasizes biophysics and biochemistry. Soon we would release its second part, since it was not possible to compile all chapters in one book. We have rigorously edited, and all authors have worked extremely hard to complete the theme in meticulous details. Readers would find a pattern in selecting the topics, a periodic feature. Let us briefly explain how eight writers have envisioned periodicity in their distinct domains of works.

Chapter 1 is written by Irena Cosic and Drasko Cosic on the protein vibrations. Irena has been developing mechanisms to build a proper theoretical model that could explain how protein vibrates to deliver key life functions. Protein is the key device for life forms.

Chapter 2 is written by Enrico Prati. There exists a scientific view that space exists and time is secondary. Based on that view, Enrico is reviewing the argument if the time or periodicity that we see is an illusion. It is a nice contrary addition to the concept explored here.

Chapter 3 is written by Danko D. Georgiev. Brain's cognition is a rhythmic process. Membrane firing is time tuned for human thoughts. What could be its origin? Deep inside neuron, there could be rhythms in the filaments, regulating the membrane above. Danko details the theory.

Chapter 4 is written by Pathik Sahoo and Subrata Ghosh. They have carried out an extensive search whether if chemical clocks are nested to regulate life. Current biology is all about highly interconnected chemical reactions. It is a new outlook to resolve rhythmic pathways.

Chapter 5 is written by Correna et al on the visual cognitive system. This chapter addresses a fundamental feature of cognition, bio-inspired visual devices, and associated technologies. Human cognition could be achieved via bionic eyes connected to higher-level intelligent devices.

Chapter 6 is written by M. V. Altaisky and N. E. Kaputkina on quantum neural network. Quantum properties are those features that add new information to the classical understanding of a phenomenon. A neuron being a classical device could harness quantum technologies. Authors have built a rigorous and robust theory for that.

Chapter 7 is written by Iain Pinder and Jonathan J. Crofts. They have addressed synchronization of periodic oscillations and clocks in a neural network. Human brain is intelligent because neurons edit time gap between spikes extremely precisely. Origin of that technology is explored here.

Chapter 8 is written by Dirk K. F. Meijer et al. He has proposed a new way of looking into the proposition of quantum consciousness. Normally, we try to add additional properties in a classical neural network property to proclaim quantum features in the brain. However, Meijer proposes that thoughts and consciousness emerge from quantum superfluids, where all information is poured in. A fantastic journey to end the book.

We hope eight completely different topics, all related to different distinct perspectives of biophysics and biochemistry would trigger a new generation of debates.

Jaipur, India — Kanad Ray
Tsukuba, Japan — Anirban Bandyopadhyay

Contents

About the Editors

Dr. Anirban Bandyopadhyay is a Senior Scientist at the National Institute for Materials Science (NIMS), Tsukuba, Japan. He completed his Ph.D. in Supramolecular Electronics at the Indian Association for the Cultivation of Science (IACS), Kolkata, 2005. From 2005 to 2008, he was an independent Researcher, as an ICYS Research Fellow at the International Center for Young Scientists (ICYS), NIMS, Japan, where he worked on the brain-like bio-processor building. In 2008, he joined as a Permanent Scientist at NIMS, working on the cavity resonator model of human brain and design synthesis of brain-like organic jelly. From 2013 to 2014, he was a Visiting Scientist at the Massachusetts Institute of Technology (MIT), USA. He has received several honors, such as the Hitachi Science and Technology Award 2010, Inamori Foundation Award 2011–2012, Kurata Foundation Award, Inamori Foundation Fellow (2011–), and Sewa Society international member, Japan. He has patented ten inventions (i) a time crystal model for building an artificial human brain, (ii) geometric-musical language to operate a fractal tape to replace the Turing tape, (iii) fourth circuit element that is not memristor, (iii) cancer & alzheimers drug, (iv) nano-submarine as a working factory & nano-surgeon, (vi) fractal condensation-based synthesis, (vii) a thermal noise harvesting chip, (viii) a new generation of molecular rotor, (ix) spontaneous self-programmable synthesis (programmable matter), and (x) fractal grid scanner for dielectric imaging. He has also designed and built multiple machines and technologies, (i) THz-magnetic nano-sensor (ii) a new class of fusion resonator antenna, etc. Currently, he is building time crystal-based artificial brain using three ways, (i) knots of darkness made of fourth circuit element, (ii) integrated circuit design, and (iii) organic supramolecular structure.

Dr. Kanad Ray is a Professor and Head of the Department of Physics at the Amity School of Applied Sciences Physics Amity University Rajasthan (AUR), Jaipur, India. He has obtained M.Sc. and Ph.D. degrees in Physics from Calcutta University and Jadavpur University, West Bengal, India. In an academic career spanning over 22 years, he has published and presented research papers in several national and international journals and conferences in India and abroad. He has

authored a book on the Electromagnetic Field Theory. Professor Ray's current research areas of interest include cognition, communication, electromagnetic field theory, antenna & wave propagation, microwave, computational biology, and applied physics. He has served as Editor of Springer Book Series such as AISC and LNEE and an Associated Editor of Journal of Integrative Neuroscience published by IOS Press, Netherlands. He has established an MOU between his University and University of Montreal, Canada, for various joint research activities. He has also established MOU with National Institute for Materials Science (NIMS), Japan, for joint research activities and visits NIMS as a Visiting Scientist. He had been Visiting Professor to Universiti Teknologi Malaysia (UTM) and Universiti Teknikal Malaysia Melaka (UTeM), Malaysia. He had organized international conference series such as SoCTA, and ICOEVCI as General Chair. He is a senior member of IEEE and an Executive Committee member of IEEE Rajasthan. He has visited Netherlands, Turkey, China, Czechoslovakia, Russia, Portugal, Finland, Belgium, South Africa, Japan, Malaysia, Thailand, Singapore, etc., for various academic missions.

Chapter 1
Macromolecular Resonances

Irena Cosic and Drasko Cosic

1 Introduction

Constant changes are everywhere in the nature. Majority of them are rhythmic, meaning regular recurrence or pattern in time that can apply to wide variety of cyclical natural phenomena having periodicity or frequency of anything from fraction of seconds to several minutes, even hours or at most extreme over many years. Besides natural rhythms, there are also man maid rhythms, where the music is the well-known example. Rhythms also play crucial role in biology including: circadian rhythm (daily physiological changes), heart activity within the frequency range of 0.5 Hz, brain activity within the frequency range of 1–100 Hz, muscular activity about 100 Hz and resonances within cellular and molecular elements ranging from MHz to THz, where biological damage occurs at frequencies higher then PHz. Here, we concentrate on rhythms and resonances within biological macromolecules, particularly those resonances relevant to macromolecular biological functions.

Over last few decades, we have discovered that crucial driving force for macromolecules (protein, DNA and RNA) activation and interaction is resonant electromagnetic energy transfer at specific frequency unique for specific activation and interaction. Based on this finding, we have developed Resonant Recognition Model (RRM) [3, 4], which is able to calculate these frequencies from periodicities within the distribution of energy of delocalised electrons along protein, DNA and/or RNA molecules using charge velocity through these macromolecules. We have applied this concept on number of proteins, DNA and/or RNA examples [1, 3–5], as well as

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on some medical conditions like: Crigler–Najjar syndrome [6], pain [7] and influence of environmental light to health [8]. This concept has been also experimentally tested by predicting the electromagnetic frequencies for activation of l-lactate dehydrogenase [9] and has been tested independently on experimental measurements of photon emission from dying melanoma cells [10], on photon emission from lethal and non-lethal Ebola strains [11], as well as on differentiation of osteoblasts stem cells [12].

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. Thus, the RRM model is promising tool for design and development of new techniques in pharmacology, drug design, biotechnology, medicine and even electronics.

2 Resonant Recognition Model (RRM)

Proteins and DNA/RNA are the main macromolecules in any living organism that are crucial for control and execution of majority biological processes within any living organism. Proteins are the main work forces, while DNA keeps all information about any biological organism and transfers this information through RNA to proteins. The Resonant Recognition Model (RRM) represents whole new view to biomolecular interactions, in particular protein–protein and protein–DNA interactions [3, 4].

The RRM is based on the finding that certain periodicities (frequencies) within distribution of energies of delocalised electrons along a protein molecule are critical for protein biological function and/or interaction with its target. The RRM enables these frequency characteristics to be calculated. These findings can be applied to the:

(a) Definition of protein or DNA functions;
(b) Definition of protein or DNA targets and analysis of their mutual recognition;
(c) Prediction of amino acids in the protein or nucleotides in the DNA which are mostly important for the function of the macromolecule;
(d) Prediction of functionally relevant mutations in proteins and/or DNA;
(e) Design of a completely new peptides or DNA fragments with desired spectral characteristics and consequently corresponding biological activities been designed.

All these RRM applications have been experimentally tested on number of examples including de novo design of Fibroblast Growth Factor (FGF) analogues [13], Human Immunodeficiency Virus (HIV) envelope mimicking peptides [14–16], and Myxoma virus analogues [17, 18].

2.1 Resonances in Proteins and DNA/RNA as Calculated by RRM Model

All proteins and DNA/RNA can be considered as linear sequence of their constitutive elements, i.e. amino acids or nucleotides and their biological function is determined primarily by the linear sequence of their constitutive elements. The Resonant Recognition Model (RRM) interprets this linear information by transforming macromolecular sequence into a numerical series and then into the frequency domain using digital signal processing methods, the Fourier transform.

In the RRM model, the protein primary structure is presented as numerical series by assigning a physical parameter value relevant to the protein's biological activity to each amino acid. Although a number of amino acid indices have been found to correlate in some ways with the biological activity of the whole protein, our investigations have shown that the best correlation can be achieved with parameters which are related to the energy of delocalised electrons of each amino acid [19, 20]. These findings can be explained by the fact that the electrons delocalised from the particular amino acid have the strongest impact on the electronic distribution of the whole protein. Within the RRM, the energy of delocalised electrons is calculated as the electron–ion interaction pseudopotential (EIIP) of each amino acid residue using the following semiempirical formula as developed by Veljkovic [21, 22]:

$$< k + q|w|k >= 0.25Z \ \sin(\pi 1.04Z)/2\pi \qquad \text{(v)}$$

where q is change of momentum of delocalised electron in the interaction with potential w, while Z is average valence number over the whole amino acid residue. The resulting numerical series represents the distribution of the free electron energies along the protein molecule.

At the second stage, the numerical series are analysed by digital signal analysis methods, using Fourier transform, in order to extract information pertinent to the biological function. The average distance between amino acid residues in a polypeptide chain is about 3.8 Å and it can be assumed that the points in the numerical sequence derived are equidistant. For further numerical analysis, the distance between points in these numerical sequences is set at an arbitrary value $d = 1$. Therefore, the maximum frequency in the spectrum is $F = 1/2d = 0.5$. The total number of points in the sequence influences the resolution of the spectrum only. Therefore, for N-point sequence, the resolution in the spectrum is equal to $1/N$. The n-th point in the spectral function corresponds to the frequency $f = n/N$.

In order to extract common spectral characteristics of sequences having the same or similar biological function, the cross-spectral function is used. Peak frequencies in the amplitude cross-spectral function define common frequency components of the two sequences analysed. To determine the common frequency components for a group of protein sequences, we have calculated the absolute values of multiple cross-spectral function coefficients for the whole group.

Peak frequencies in such multiple cross-spectral function present common frequency components for all sequences analysed. Signal-to-noise ratio S/N for each peak is defined as a measure of similarity between sequences analysed. The S/N is calculated as the ratio between the signal intensity at the peak frequency and the mean value over the whole spectrum. Previous research results have shown that the value of S/N ratio of at least 20 can be considered as significant [3, 4]. The multiple cross-spectral function of large group of sequences with the same biological function is called "consensus spectrum". The presence of a peak frequency with the significant signal-to-noise ratio in a consensus spectrum implies that all the analysed sequences within the group have one frequency component in common. This frequency is related to the biological function provided the following criteria are met:

(a) one peak only exists for a group of protein sequences sharing the same biological function
(b) no significant peak exists for biologically unrelated protein sequences
(c) peak frequencies are different for different biological functions.

Above criteria have been implemented throughout the sequence databases [3, 4] and the following fundamental conclusion was drawn:

Each specific biological function within protein or DNA is characterised by one frequency.

The comprehensive analysis done so far confirms that all protein sequences with the common biological function have common frequency component, which is specific feature for the observed function/interaction [1, 3–8, 23–25] . In order to understand the meaning of the characteristic frequency, it is important to clarify what is meant by the biological function of proteins. Each biological process is driven by proteins that selectively interact with other proteins, DNA regulatory segment or small molecules. These interactive processes that involve energy transfer between the interacting molecules are highly selective. How is this selectivity achieved? In the RRM, it is assumed that the selectivity is defined within the amino acid sequence. It has been shown that proteins and their targets share the same characteristic frequency [3, 4, 23, 24], as presented in case of leptin–leptin receptor interaction in Fig. 1. However, there is opposite phase (phase difference close to 3.14 rad) at this characteristic frequency for each pair of interacting macromolecules, as presented in case of leptin–leptin receptor interaction in Fig. 2.

Having all above in mind, we conclude that RRM characteristic frequencies represent proteins' general functions, as well as mutual recognition between protein and its target (receptor, ligand, etc.). These results from matching of periodicities within the distribution of energies of free electrons along the interacting proteins, can be regarded as the resonant recognition. Therefore, it has been proposed that interacting molecules "communicate" with each other, i.e. recognise each other at the distance, based on the same/similar characteristic frequency. Thus, these frequencies must represent oscillations of some physical field which can transmit through water dipoles. One of the possibilities is that this field is electromagnetic in nature [1, 3–5].

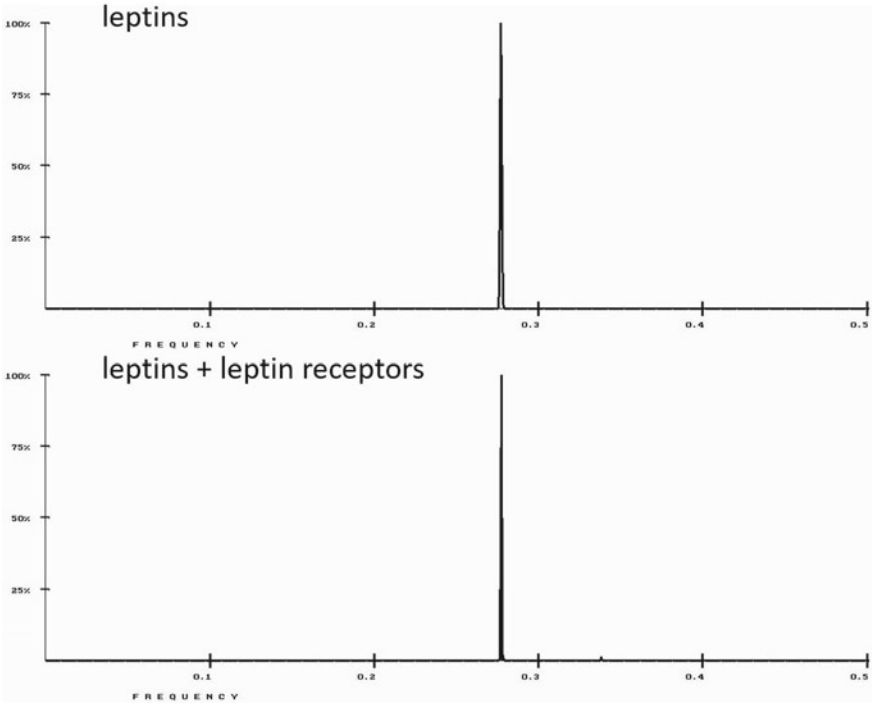

Fig. 1 Cross-spectrum of leptins and leptin–leptin receptors identifying the common characteristic RRM frequency of 0.2764 [24]

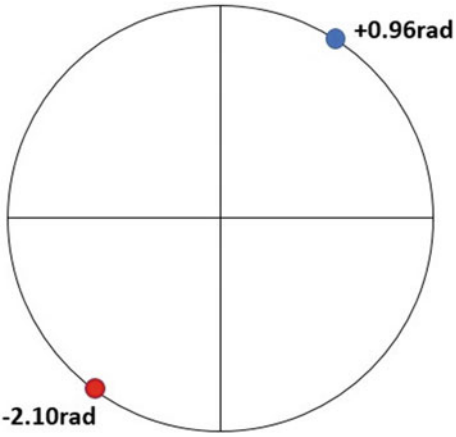

Fig. 2 Phase circles at RRM frequency of 0.2764 for human leptin protein (+0.96 rad) in blue and human leptin receptor protein (−2.10 rad) in red. It can be easily observed that these phases are opposite to each other, supporting the RRM approach that protein and protein receptors should have opposite phases at RRM frequency characterising their recognition and interaction. Phases at leptin–leptin receptor characteristic RRM frequency approximately opposite with phase difference of 3.06 rad [24]

2.2 Electromagnetic RRM Resonances Relevant to Biomolecular Biological Functions

The RRM proposes that protein and DNA/RNA activations and interactions entail mechanism of resonant energy transfer between involved macromolecules at the frequency specific for each observed function/interaction [3, 4]. This proposal is based on the findings that certain periodicities within the distribution of energy of delocalized electrons along protein molecule are critical for protein biological function and/or interaction with their targets [3, 4]. If charge transfer through these macromolecules is introduced, then charge moving through macromolecular backbone can produce electromagnetic radiation, absorption and resonance with spectral characteristics corresponding to the energy distribution [3, 4].

Since there is evidence that proteins and DNA have certain conducting or semiconducting properties, 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 charge velocity through protein backbone could be estimated from potential difference between COOH and NH_2 ends of protein. According to the EIIP pseudopotential theory [21, 22], this potential energy difference is:

$$W = W(\mathrm{COOH}) - W(\mathrm{NH_2}) = 0.13\mathrm{Ry}$$

This energy difference allows for maximum velocity of charge, which is equal to:

$$V_{\max} = \sqrt{(2\mathrm{eW/m})}$$

where e represents the electron charge and m represents the electron mass. Therefore:

$$V < 7.87 \times 10^5 \mathrm{m/s}$$

Thus, the RRM proposes that the charge is travelling through the macromolecular backbone at the estimated velocity $V = 7.87 \times 10^5$ m/s [1, 3, 4]. For this velocity and with the distance between amino acids along the protein backbone $d = 3.8$ Å, the maximum frequency that could be emitted during this electron transfer is $F_{\max} = V/(2d) \approx 10^{15}$ Hz, while the minimum frequency that could be emitted depends on the length of the protein $F_{\min} = 2F_{\max}/N$, where N is the total number of amino acids within the protein. For example, for protein of 200 amino acids in length, the minimum frequency is $F_{\min} \approx 10^{13}$ Hz. Thus, the frequency range of protein interactions was estimated to be in the range between 10^{13} Hz and 10^{15} Hz [1, 3, 4], including far infra-red, infra-red and visible up to ultra-violet light spectrum. To support this idea, we compared our computational predictions with number of published experimental results [3, 4]:

- Laser light growth promotion of cells, by using the particular frequencies of light to produce the similar effect to that of growth factor proteins;
- Chymotrypsin activation (increase of enzyme activity) achieved by laser light radiation in a range of 850–860 nm;
- Activation of highly homologous plant photoreceptors which, although being very homologous, absorb different wavelengths of light;
- Photoactivated proteins, e.g. rhodopsin, flavodoxin, etc.

These comparisons have shown a strong linear correlation between frequencies, as calculated using the RRM method and experimentally measured characteristic frequencies, with the slope factor of $K = 201$ [3, 4]. This finding parallels with the frequency range previously associated with the RRM numerical frequency spectrum that has been calculated from the charge velocities through the protein backbone. This correlation can be represented as following:

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

where λ is the wavelength of light irradiation in nm, which can influence a 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-selective interactions, biological processes and pathways in living cells. In our previous work, we calculated large number of specific frequencies for different protein and DNA biological functions and interactions [1, 3–5, 8, 24, 25], as presented in Fig. 3. In addition, although biological processes are currently looked as large number of different events, we have shown that they are grouped in relatively small number of general functions (functional super families) enabling the simpler approach to understanding macromolecular interactions, biological functions and related health effects [8, 24, 25]. Functional super families are differently coloured and labelled in Fig. 3.

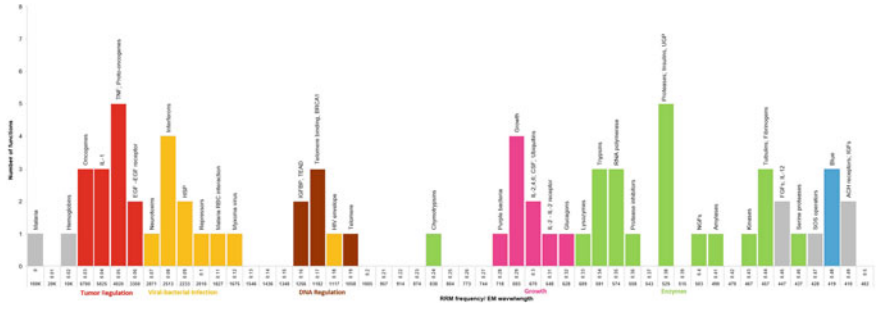

Fig. 3 Number of functional groups within each Resonant Recognition Model (RRM) frequency range of 0.01. *X*-axis represents RRM frequency in steps of 0.01, as well as corresponding electromagnetic frequency in nm. *Y*-axis represents the number of functional groups. Names of functional groups are written on the top of each bar. Functional super families are differently coloured and labelled below the *X*-axis

The RRM concept, proposing that specific frequencies of electromagnetic radiation are critical for macromolecular activities and interactions, has been experimentally tested on electromagnetic frequencies activating l-lactate dehydrogenase [9], photon emission from dying melanoma cells [10], photon emission from lethal and non-lethal Ebola strains [11], JAK-STAT signalling pathway [26], as well as more recently on osteoblastic differentiation of stem cells by photobiomodulation [12]. Even more, the RRM model, for the first time, explains how and why external blue light can be used in treatment of Crigler–Najjar syndrome [6]. This means that, by radiating the whole body with specific RRM frequency, the desired health and medical effects can be achieved.

Keeping all this in mind, we propose that the RRM concept is excellent predictor for proteins and DNA/RNA selective interactions, biological processes and pathways in living cells.

2.3 Electromagnetic RRM Resonances Relevant in Electronics

So far, we have presented above the possibility of electromagnetic resonances within protein, DNA and/or RNA relevant for their biological functions. These resonances are based on charge velocity through macromolecular backbone of $V = 7.87 \times 10^5$ m/s [3, 4] and consequently producing electromagnetic radiation within range of far infra-red, infra-red and visible up to ultra-violet light spectrum. However, there are additional possible electromagnetic resonances in proteins that can be related, not only to their biological function, but also to some other properties of proteins, which can be important for some technological applications. Such resonances could be within different frequency ranges of electromagnetic radiation based on different charge velocity, but with the same distribution of free electron energies along the protein. We have examined these possibilities on example of tubulin [1].

Tubulin and microtubules have been extensively researched in two directions. One direction is towards an idea that these macromolecules are essential element of brain cells processing information as proposed by Hameroff [27]. He proposes that microtubules quantum states of decoherence are essential element for neurophysiological effects. However, there is no agreement on velocity and frequency of this decoherence in regard to velocity of neurological effects. While Tegmark proposes that these processes are in order of decoherence time of 10^{-13} s [28], Hameroff argues that these processes are much slower [27].

Consequently, there has been a proposal that "microtubules can act as macromolecular computer with phonon-coupled tubulin dipole states functioning as bits interacting/computing with neighbouring tubulin bit states in microtubule (cellular) bit automata" [29]. For this purpose, it is important to investigate resonances in tubulin [30].

The second direction of research is towards the understanding tubulin biological function in cells other than the brain cells and in particular tubulin's possible role in cell division in relation to division of cancer cells. Interest in tubulin structure and function increased when taxol, which binds to microtubules, was found to be effective treatment for a number of cancers. By binding to microtubules and causing them to become more stable, taxol prevents cell division and thus blocks cancer growth [31].

To analyse all possible resonances for both directions of tubulin research, we have applied the RRM model for different possible velocities of charge transfer along protein. As described above, the RRM method is based on the finding that certain periodicities (frequencies) within distribution of energies of delocalized electrons along protein molecule are critical for protein biological function and/or interaction with its target [3, 4]. If protein conductivity was introduced, then charge moving through protein backbone can produce electromagnetic irradiation or absorption with spectral characteristics corresponding to energy distribution along the protein. The RRM method enables these spectral characteristics to be calculated. These frequencies depend on charge velocity. Initially, charge velocity was considered to travel only through the protein backbone when the frequencies were found to be in the range from far infra-red, infra-red and visible up to ultra-violet light spectrum [1, 3–5, 8, 12]. When different charge movement modalities (velocities) were applied to the whole protein 3D structure (not backbone only), other possible resonant frequency ranges were identified [1]. We applied the charge velocity in the forms of solitons, excitons and phonons, which may travelled through the 3D structure of proteins, in particular through the alpha helix. In these instances, protein resonant frequencies have much wider spectrum, ranging from KHz to THz [1]. This enabled completely new view to protein resonances that could be particularly relevant to tubulin activity as quantum information communication system (macromolecular computer).

As shown above, the RRM characteristic frequencies calculated from protein sequence can be related to their electromagnetic frequencies if there is charge travelling along the protein sequence. Initially, we proposed that charge (most probably electrons) is travelling through protein backbone with the velocity of 7.87×10^5 m/s. For this velocity and the distance between amino acids in a protein molecule, which is 3.8 Å, the frequency range obtained for protein interactions was estimated to be in the range between 10^{13} and 10^{15} Hz.

However, if we take into account the complex structure of proteins and in particular, alpha helices, the charge transfer is also possible to occur through these 3D structures, different charge transfer modalities can be applied, and the range of possible resonant frequencies can be extended. We considered the following charge transfer modalities: solitons (Davydov [32, 33], Hayman [34], Sinkala [35]), excitons (Davydov [32, 33], Sinkala [35], Pang [36], Yomosa [37]) and phonons (Pang [36], Yomosa [37], Ichinose [38]). These other forms of charge transfers are at different velocities ranging from 10^5m/s for solitons and some excitons to the speed of sound and small fractions of speed of sound for phonons. Therefore, with the same numerical characteristic frequencies calculated using the RRM method, different modalities of charge transfer can produce different resonant electromagnetic frequencies, which

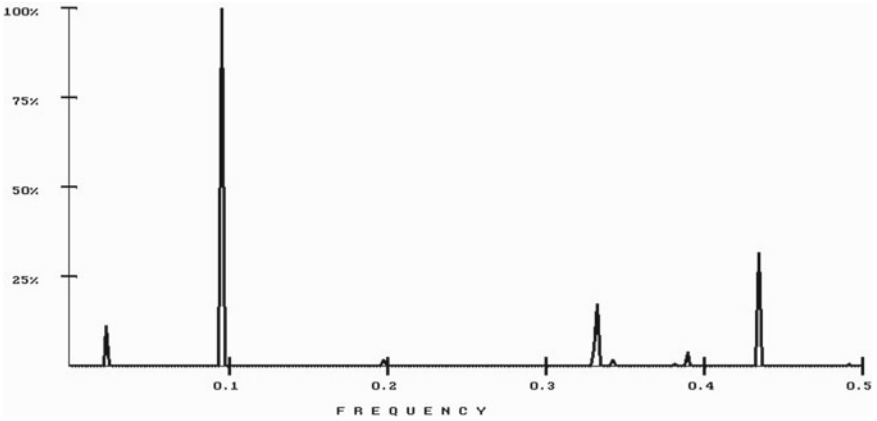

Fig. 4 Cross-spectrum for mammalian tubulin alpha and beta chains together calculated using the RRM method [1]

are not necessarily related to the protein biological function but could be related to protein resonances in general. When numerical cross-spectra RRM calculations have been applied to alpha and beta tubulins, the main common frequency was found to be at 0.0957, as presented in Fig. 4 [1].

This frequency of 0.0957 represents the characteristic periodicity in distribution of energies of free electrons along protein for all analysed tubulins. With the same periodicity of energy distribution, but different velocities due to different modalities of charge transfer, the different resonant frequencies have been obtained as presented in Table 1.

These results have shown that possible resonant frequencies in tubulin molecules can be within different frequency ranges (THz, GHz, MHz and even KHz) depending on mechanism and charge velocity within the protein structure.

These results have been viewed in the light of the theory proposed by Hameroff and Tuszynski et al. [39–41] where they compare coherent energy transfer between aromatic rings in tubulin and microtubules to quantum conductance through photosynthesis. Such process is explained by mechanical vibration in microtubules. Microtubules appear to have their own set of mechanical vibrations as proposed by Anirban Bandyopadhyay [42, 43] which are called "Bandyopadhyay coherence—BC". Bandyopadhyay is suggesting that quantum effects occurred in microtubules as electronic conductance along microtubules became extremely high, close to quantum conductance, at certain specific resonant frequencies. These resonances are consistent with the intra-tubulin aromatic ring pathways in THz ranges, as well as quantum effects proposed by Bandyopadhyay which occur in GHz, MHz and KHz ranges and are particularly prominent in low MHz range (e.g. 8.9 MHz) [42, 43]. When compared with our results [1], these mechanical vibrations could be particularly related to phonon velocities as proposed by Ichinose [38]. In addition, Bandyopadhyay suggested that there is the whole range of resonances in a single microtubule

Table 1 Different resonant frequencies for different charge transfer modalities [1]

RRM frequency	Velocity RRM 7.78×10^5 m/s	Velocity Yomosa 3.2 m/s	Velocity Yomosa 1.2×10^5 m/s	Velocity Pang 68 m/s	Velocity Davydov 170 m/s	Velocity Ichinose 0.34 m/s	Velocity Ichinose 5×10^{-4} m/s
0.0957	97–101 THz	392–411 MHz	14–16 THz	8–9 GHz	21–22 GHz	40–42 MHz	60–62 KHz

from 1 kHz to 1.3 GHz with the most prominent peaks at: (a) around 15 kHz, (b) within range of 9–30 MHz and (c) within range of 86–228 MHz [42]. These results are again comparable with our results for velocities of phonons [1], as proposed by Ichinose [38]. However, our results extend to much higher frequencies in GHz and THz ranges. This suggests that these higher frequencies, which are not related to phonon velocities, but are related to velocities of solitons and excitons, are not mechanical, but pure electromagnetic in nature.

3 RRM Bioresonances in Biology and Medicine

There is much evidence of existence of electromagnetic resonances within biological macromolecules, particularly proteins and DNA/RNA. The whole area of biophotonics is related to ultra-weak photon emission from biological systems [44], particularly within the range of UVA, visible and infra-red spectrum. In addition, there is also evidence of biomolecular resonances in much lower frequency ranges including KHz, MHz and GHz. However, so far there is no evidence or theory, how and if these macromolecular resonances are related to biological activity of macromolecules.

Here we present, the Resonant Recognition Model (RRM), which can explain that such emission, and particularly its specific frequencies, are critical for resonant activation of proteins and DNA/RNA. The RRM is based on the findings that certain periodicities within the distribution of energy of delocalized electrons along protein (DNA/RNA) molecule are critical for their biological function and/or interaction with their targets [3, 4, 23, 24]. If charge transfer through these macromolecules is introduced, then charge moving through macromolecular backbone can produce electromagnetic radiation, absorption and resonance with spectral characteristics corresponding to energy distribution. The frequency range of this radiation depends on charge velocity [3, 4]. We applied this concept on number of proteins and DNA/RNA examples, as well as on some medical conditions like: Crigler–Najjar syndrome [6], pain and influence of environmental light to health [8]. This concept has been also experimentally tested by predicting the electromagnetic frequencies for activation of l-lactate Dehydrogenase [9]. The concept has also been tested independently on experimental measurements of photon emission from dying melanoma cells [10], as well as on photon emission from lethal and non-lethal Ebola strains [11].

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. Thus, the RRM approach is promising tool for design and development of new techniques in pharmacology, drug design, biotechnology and medicine.

3.1 Interactions Between Proteins and DNA/RNA

The RRM is unique model that is capable to analyse directly activities and interactions of proteins, DNA and RNA by identifying their characteristic frequencies. One example is analysis of interaction between telomere (DNA), telomerase (protein) and telomerase binding region (RNA), all of which are involved in cellular ageing process. Biological ageing at the cellular level was always puzzling scientists. It is well known that any mature cell can divide only certain number of times before stop dividing and eventually die. The main part in this process is due to telomeres, which are made up of many kilo bases of DNA repeats (TTAGGG) at the end of each chromosome and, bound and protected by telomere binding protein [45, 46]. Each time when cell divides, the chromosomes of the new cell are shorter at the ends making telomeres shorter. When telomeres get too short, the cell can no longer divide, becomes inactive and dies. If there would not be telomeres at all, the main genetic information in chromosomes will become shorter with each cell division and the genetic information will be then lost and corrupted [45, 46].

In contrast to process of shortening telomeres, enzyme telomerase can add nucleotides to the end of telomeres. Telomerase is composed of reverse transcriptase (TERT) and an RNA component (TERC) that serves as template for telomere elongation [45, 46]. In somatic cells, there is not enough telomerase to keep telomeres from eventual wearing down producing cells ageing, inactivity and eventual death [45, 46]. In cancer cells, which divide much more often than normal cells, telomeres get very short. However, these cells very often produce telomerase enzyme which prevents telomeres to get too short and thus prevents cell from dying [45, 46].

By applying the RRM model, we have investigated interactions between participants in process of telomere shortening and/or elongation including telomeres, telomerase and telomere binding proteins [5, 47]. When human telomeres (DNA) from different human chromosomes were compared the common RRM characteristic frequency is at 0.1875 within wide spectrum range of 0.17–0.19, as presented in Fig. 5 top.

Interestingly when all participants in telomeres activity binding and elongation were compared, no matter if they are proteins, DNA or RNA as possible by the RRM model, the same common characteristic frequency was obtained at 0.1875 within wider spectrum range of 0.17–0.19, as presented in Fig. 5 bottom.

This result is significant showing that all participants in telomere related cellular ageing are having common RRM characteristic frequency. This result can be significant in further understanding of cellular ageing. In addition, this is excellent example demonstrating capability of RRM model to analyse and compare activities and interactions of proteins, DNA and RNA.

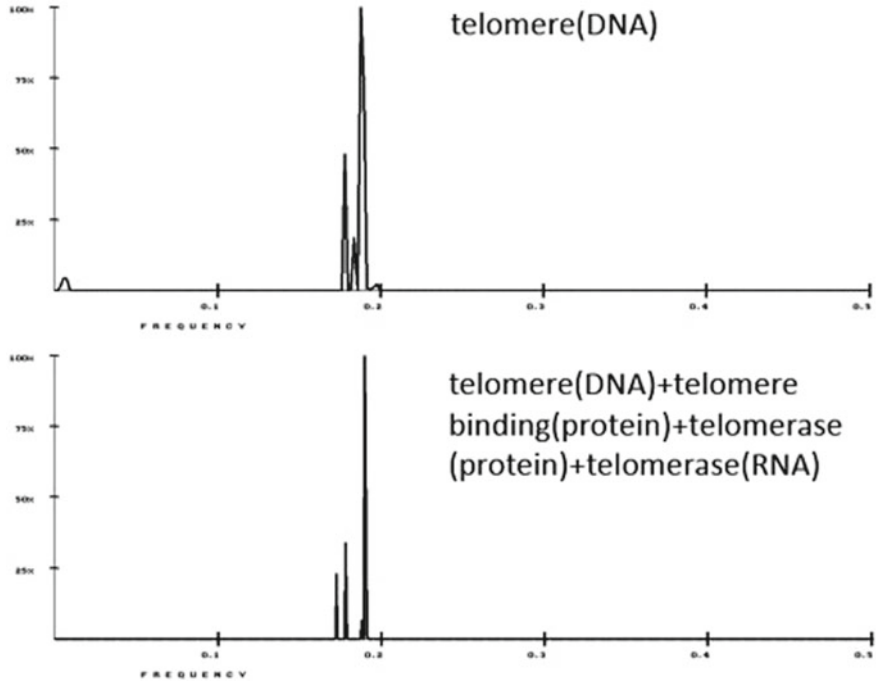

Fig. 5 Top: RRM cross-spectrum for human telomere (DNA); Bottom: RRM cross-spectrum for telomere (DNA), telomere binding protein (protein), telomerase (protein) and telomerase (RNA). The common RRM characteristic frequency for telomeres and telomere related macromolecules has been identified at 0.1875

3.2 Drug Design

There is large multi-billion biotechnology industry mostly developing new drugs for various diseases that are not yet successfully treated. These developments are usually based on testing of large number of compounds/molecules without complete understanding of their activity, specificity and side effects. As such tapping in the dark developments are time consuming, expensive and very often do not lead to desired results, there is need for better understanding of biomolecular activity and specificity. The most important group of biomolecules are proteins, which are the main biomolecular forces that are involved in controlling most biological processes in living cells, tissues and organisms. They exhibit their biological functions through selective interactions with other molecules, which could also be proteins and/or DNA. The most complex protein interactions are interactions between proteins and their receptors, which are proteins or complexes of proteins that selectively drive specific biological pathways. Currently, the selectivity of interactions between proteins and their receptors is investigated mostly using 3D matching between interacting proteins, which

is not explicit enough to explain the high specificity of these interactions. Experimentally, protein–receptor interactions are investigated by number of techniques including X-ray, MRI, spectroscopy, etc. However, all these techniques are very expensive and time consuming. Thus, there is need for biophysical approach that can investigate protein–receptor interactions with more specificity than 3D matching. The RRM model is capable to analyse activity and specificity of protein interactions by calculating characteristic frequency and phase for each specific biological interaction and activity. Once when we know that each biological function/interaction is characterised with RRM frequency and phase, we can use this parameter to analyse protein biological function, predict key amino acids ("hot spots") for the particular function and even design de novo peptides/proteins with the desired biological function or interaction ability.

Knowing the characteristic frequency of a particular protein function creates the possibility to predict which amino acids prevail in the sequence and predominantly contribute to this frequency and consequently to the observed function. This could be achieved by small alternations of amplitude in single protein spectrum at characteristic frequency and then observing which amino acids are mostly sensitive to this alternation [3, 4, 23, 48–50]. These sensitive amino acids ("hot spots") are related to characteristic frequency and consequently to the corresponding biological function. The "hot spots" predictions, using the RRM, have been applied already to a number of protein and DNA examples including interleukin-2, SV40 enhancer, epidermal growth factor EGF, Ha-ras p21 oncogene product, glucagons, haemoglobins, myoglobins and lysozymes [3, 4, 23, 48–50].

It has been experimentally documented at the example of influenza virus that such predicted amino acids denote residues crucial for protein function [51]. In addition, these "hot spots" amino acids are found to be spatially clustered in the protein tertiary structure and to be positioned in and around the protein active site [48–50].

Once the characteristic biological function of the protein is identified, it is possible to design new proteins with desired frequency components and consequently with desired biological functions [3, 4, 13–15, 52–55]. The process of bioactive peptides design is as follows:

1. Determination of RRM characteristic frequency using multiple cross-spectral function for a group of protein sequences that share common biological function (interaction);
2. Determination of phases for the characteristic frequencies of a particular protein which is selected as the parent for agonist/antagonist peptide;
3. Calculation using inverse Fourier transform of the signal with characteristic frequency and phase. The minimal length of the designed peptide is defined by the characteristic frequency f as $1/f$;
4. Determination of resulting amino acid sequence using tabulated EIIP parameter values.

This approach has been already successfully applied and experimentally tested in design of FGF [13], HIV envelope protein analogue [14–16] and peptide to mimic myxoma virus oncolytic function [17, 18].

For example, in the case of Fibroblast Growth Factors, two characteristic frequencies were identified: one related to receptor recognition and another related to "growth activity". The aim of that project was to design peptide which can competitively bind to the FGF receptor but without inducing growth. Using only receptor recognition frequency, the 16-mer peptide was designed, experimentally tested and indeed had receptor recognition activity without inducing growth [13].

In the case of HIV virus, the one common RRM frequency was identified for all HIV envelope protein despite their high variability. This frequency was used to design peptide that can immunologically mimic all HIV isolates and thus could be a good candidate for vaccine [14–16].

Similar idea as described above was used to mimic myxoma virus oncolytic function. Myxoma virus (MV) is a rabbit-specific poxvirus pathogen that also exhibits a unique tropism for human tumour cells and is dramatically oncolytic for human cancer xenografts. The RRM characteristic frequency for MV proteins was identified and used to design peptides that were experimentally shown to mimic myxoma virus oncolytic function [18].

It is important to note that de novo designed peptides/proteins do not have any significant homology with the original protein but have the same RRM characteristic frequency and related biological function. This is like in music, when you can recognise the same melody even when written with different notes.

3.3 Photobiomodulation in Medicine

There is much evidence that electromagnetic radiation can influence human health and wellbeing. As RRM model proposes that electromagnetic radiation can influence protein activity, we propose that biomodulation health effects are based on selective activation of proteins. One example is treatment of Crigler–Najjar syndrome by blue light. The Crigler–Najjar syndrome is extremely rare genetic disease affecting the metabolisms of bilirubin, resulting in a form of non-haemolytic jaundice [56]. This disease is caused by lack of expression of UDP glucuronosyltransferase 1-A1. Hence, there is no response to treatment with phenobarbital. The only available treatment is phototherapy, which involves radiation of patients with the blue light for an extensive time every day, usually whole night. Similar treatment is used for jaundice in newborn babies.

Here, we have investigated: how and why, the specific blue light radiation can mimic activity of UDP glucuronosyltransferase 1-A1 [6]. For that purpose, we used Resonant Recognition Model and we found that specific RRM frequency for UDP glucuronosyltransferase 1-A1 biological function is within the blue light frequency range [6]. This finding explicitly explains, why the blue light can mimic and replace activity of UDP glucuronosyltransferase 1-A1.

We have analysed six HUMAN UDP glucuronosyltransferase proteins using the RRM and it has been revealed that the common frequency for all analysed sequences is at frequency of 0.3799, as presented in Fig. 6.

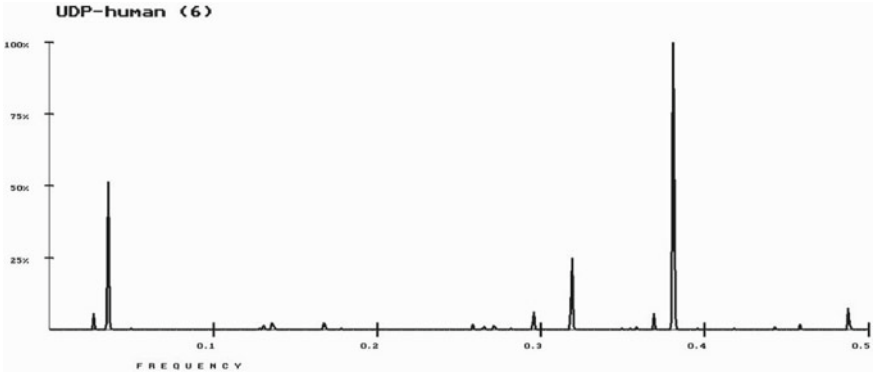

Fig. 6 Spectrum for six human UDP proteins showing prominent common peak at frequency of 0.3799

To make sure that this frequency is related to UDP function in bilirubin metabolism, we have also compared these six human UDP's with beta-barrel protein (angja) that binds bilirubin with high affinity. The result is the more prominent peak at frequency of 0.3799, as presented in Fig. 7. This confirms that frequency of 0.3799 is common to UDP's and angja proteins. According to RRM principles this numerical frequency is related to electromagnetic radiation of 529 nm, which is within blue visible light spectrum [6].

As it can be seen from the results above, using the RRM model we have found that specific RRM frequency for UDP glucuronosyltransferase 1-A1 biological function is within the blue light frequency range [6]. This finding explicitly explains, why the blue light can mimic and replace activity of UDP glucuronosyltransferase 1-A1.

Along these lines, we propose that number of other diseases and syndromes could be treated by electromagnetic frequencies calculated specifically for activation of

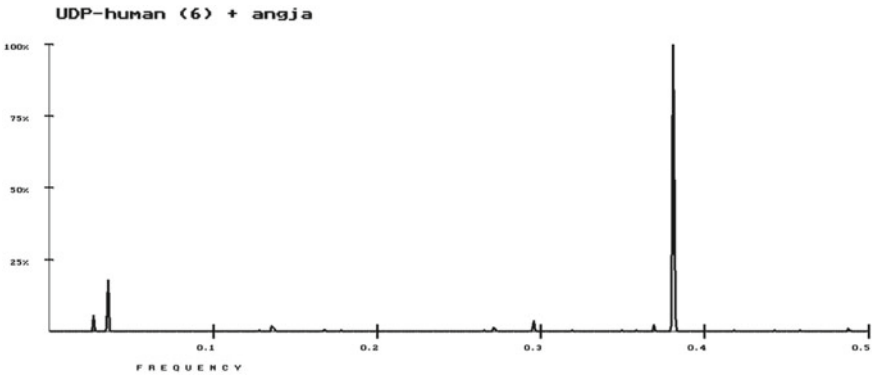

Fig. 7 Spectrum for six human UDP proteins together with angja protein showing single prominent peak at frequency of 0.3799 (529 nm)

proteins critical for those diseases and syndromes. For example, we propose that cystic fibrosis, which is genetic disease caused by mutation in CFTR protein, could be treated by electromagnetic radiation wavelength of 4527 nm corresponding to RRM frequency of 0.0444, which is mimicking healthy CFTR protein [57].

The other example is treatment of obesity by electromagnetic radiation wavelength of 727 nm corresponding to RRM frequency of 0.2764, which characterise leptin proteins that are critical for hunger control and energy balance within the body [24].

There is also possibility for cancer treatment using electromagnetic radiation predicted by the RRM model. As already established that there are two different computationally calculated RRM frequencies for oncogenes at $f_o = 0.0322$ corresponding to wavelength of 6242 nm and for proto-oncogenes at $f_p = 0.0537$ corresponding to wavelength of 3743 nm [25], as presented in Fig. 8.

It has been also shown that number of proteins involved in anticancer activity and apoptosis, like TNF and TNF receptor, are also having the RRM characteristic frequency within the range of RRM frequencies characterising proto-oncogenes f_p [23]. Thus, it is proposed that electromagnetic radiation within far infra-red spectrum related to RRM frequency f_p can induce cytotoxic effects on cancer cells. It has been shown in number of in vitro experiments that light exposure within the far infra-red range of 3500–6400 nm can induce significant cytotoxic effect on cancer cells, while the same exposure regime does not show substantial effect on normal cells

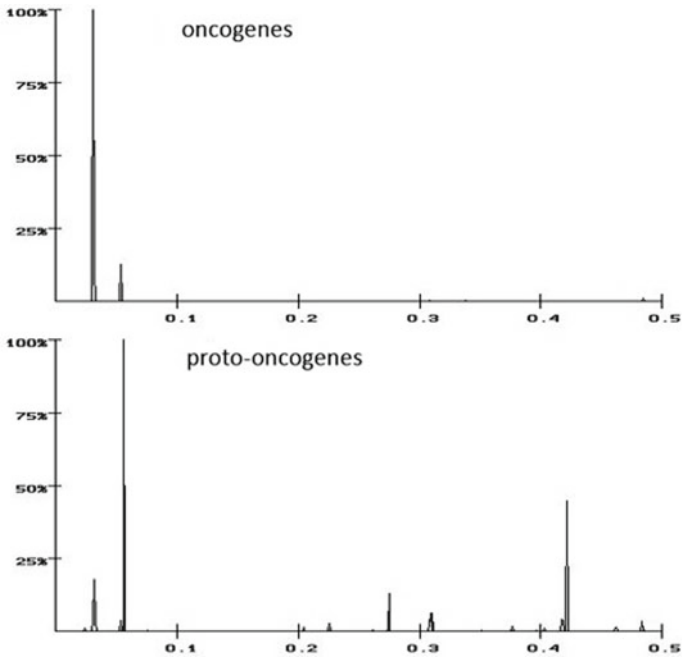

Fig. 8 RRM frequencies for oncogenes at $f_o = 0.0322$ corresponding to wavelength of 6242 nm and for proto-oncogenes at $f_p = 0.0537$ corresponding to wavelength of 3743 nm

[58]. Thus, findings from that study validate the proposed hypothesis that the RRM calculated frequencies within far infra-red spectrum can induce cytotoxic activity on cancer cells opening new path for treatment of cancer.

3.4 Stem Cell Differentiation Using Electromagnetic Radiation

There is an emerging need to use tissue engineering based on living cells as an alternative to tissue or organ transplantation. The main interest is differentiation of stem cells into osteoblasts for bone regeneration, bone healing and bone transplantation. Parathyroid hormone (PTH) is involved in the stimulation of bone remodelling and in the induction of differentiation of bone marrow mesenchymal stromal/stem cells by enhancing bone morphogenetic protein signalling [59].

The PTH is the principal regulator of calcium homaeostasis in the human body and capable to influence and expand the bone marrow stem cell niche with both self-renewal and differentiation. As it has been shown that the population of pluripotent stem cells highly express parathyroid hormone type 1 receptors, it was postulated that parathyroid hormone has similar action as stromal cell-derived factor-1 (SDF-1α), which is crucial for the recruitment of stem cells to number of diseased organs [60].

Moreover, it has been shown that photobiomodulation (PBM) of specific blue and green light wavelengths initiates osteoblastic differentiation of human adipose-derived stem cells [61]. The research described in reference [61] presents the effect of PBM on both proliferation and differentiation of osteogenic stem cells. The effects of four different wavelengths (420, 540, 660 and 810 nm) were measured and it has been shown that wavelengths of 420 and 540 nm were more efficient in stimulating osteoblast differentiation compared to wavelengths of 660 and 810 nm [61].

Here, we hypothesised that stimulation of osteoblast differentiation by specific blue and green light wavelengths is related to activation of proteins involved in osteoblast differentiation like PTH and SDF-1α. For this purpose, we have utilised the RRM model, which proposes that protein activation and function are based on specific wavelengths (frequencies) of electromagnetic radiation within far infra-red, infra-red and visible up to ultra-violet light spectrum. Thus, by using the RRM, we have analysed the parathyroid hormone, its receptor and stromal self-derived factor with the aim to predict the characteristic wavelengths (frequencies) related to parathyroid hormone activities, particularly differentiation of stem cells into osteoblasts [12].

When PTH proteins and SDF-1α proteins have been analysed together, using the RRM model, the prominent common RRM frequency was calculated at 0.3975 as presented in Fig. 9, characterising their common biological function, i.e. stem cells differentiation into osteoblasts. This RRM frequency corresponds to electromagnetic radiation wavelength of 502 nm [12].

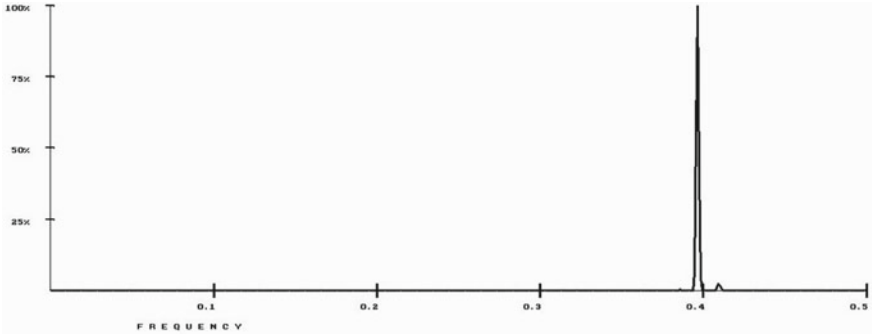

Fig. 9 RRM cross-spectrum of PTH proteins and SDF-1α proteins. The prominent common characteristic frequency is at 0.3975, which represents an electromagnetic radiation wavelength of 502 nm [12]

The presented results show that characteristic frequency for the activity of parathyroid hormone (PTH) and stromal cell-derived factor-1 (SDF-1α) related to differentiation of stem cells is at 0.3975 with corresponding electromagnetic radiation wavelength of 502 nm [12]. It is important to observe that wavelength of 502 nm is exactly between the wavelengths of 420 nm and 540 nm, which in previous experiment was found to be effective in stimulating osteoblast differentiation [61]. This indicates that specificity of wavelengths, which stimulate osteoblast differentiation, could be explained by photoactivation of proteins involved in osteoblast differentiation, as predicted by the RRM model. Even more, as the RRM model predicts that the most effective wavelength would be 502 nm [12], which is in between the already tested wavelengths of 420 and 540 nm [61], we propose that wavelength of 502 nm would induce even more efficient stimulation of osteoblast differentiation. Thus, the findings of this research can be used in development of improved techniques for differentiation of stem cells using the electromagnetic radiation of specific wavelength of 502 nm. Future research should involve validation of these results by experimental testing of stem cell differentiation.

3.5 Environmental Radiation

It is well known that the life on Earth originated and has been sustained by the electromagnetic energy from the sun light. In primitive organisms and plants, the sun light directly influences biological processes, while in more complex organisms, it has more indirect role. In these organisms, due to their more complex structure, the sun light cannot penetrate into each cell, therefore they have to create their own "internal sun" energy to drive selectivity of biological processes in their cells, in the same manner as it was originally initiated by the sun light [44, 62].