

# Influence of Tuning Element Relief Patches on Pain as Analyzed by the Resonant Recognition Model

Irena Cosic and Drasko Cosic

**Abstract**— Tuning Element Relief Patches (TERP) are silicon based Titanium Salt infused adhesive patches that have been developed by Tuning Element. A number of anecdotal reports have shown that TERP patches diffuse pain, including chronic, inflammatory and neuropathic. Pain is a very complex biochemical and electrical process involving sensory part, nerve transmission and brain perception of pain. We concentrated our research on nerve transmission, which is electrical signal along the nerve (axon). This electrical signal is created by complex activity of opening and closing of pain related ion channels and redistribution of electrically charged ions on the nerve cell membrane. Ion channels are made of different proteins, which are involved with the complex processes of opening and closing ion channels. Here, we apply Resonant Recognition Model (RRM) to analyze ion channel proteins related to the pain transmission in order to find out, how imprints and particles within TERP patches can interfere with pain related activity of ion channels.

**Index Terms** — pain, titanium salt infused patches, protein resonances, resonant recognition model, signal processing.

## I. INTRODUCTION

Pain, both acute and chronic, is debilitating medical condition that is a major cause of suffering in the general population and has significant economic impact. Often, only the pain symptoms could be treated, but not the cause. Currently, the pharmaceutical approach is used, which is costly and very often cause multiple side effects. In recent studies, it has been shown that the titanium in pico-nanometer scale and soluble form has beneficial effect on reduction of pain [1]. TERP patches are the silicon based titanium salt infused adhesive patches, which when directly applied to the pain areas, have been able to diminish pain. Phase one of the initial animal study done at Missouri State University showed the nontoxicity of TERP patches (correspondence with Prof. Durham). In addition, clinical findings on 174 “pain cases” presented with an improved pain when TERP patches were used (Dr. Brasovan TE “summit meeting” in October 2014). The pain was measured using the pain assessment scale from The National Initiative on Pain Control (0-10 Numeric Pain Rating Scale).

These clinical studies have suggested that TERP patches can offer a safe and cost-effective pain management.

Pain is very complex biochemical and electrical process involving sensory part, nerve transmission and brain perception of pain [2]. Pain is travelling along the nerves (axons) in shape of action potential going to dorsal root ganglia’s, where it is processed in spinal dorsal horn and it is transferred through spinal nerves to brain where perception of pain is processed [2]. Here, we concentrated on the nerve transmission which is in fact electrical signal along the nerve (axon). This electrical signal is formed by complex activation (opening and closing) of specific pain related ion channels and the redistribution of electrically charged ions at nerve cell membrane. Ion channels are made of number of proteins that are involved and control these complex processes of opening and closing ion channels [3]. Activity of sodium ion channels is the most critical for pain transmission along nerves. “Proteins in ion channels mediate the voltage-dependent ion permeability of excitable nerve cell membranes. Assuming open or close conformations in response to the voltage difference across the membrane, proteins form a sodium-selective channel through which Na<sup>+</sup> ions may pass in accordance with their electro chemical gradient. These ion channels play critical role in pain mechanisms” [4]. In addition, there is a specific role for calcium ion channels in pain transfer along the nerve in the similar manner [2].

Acute, inflammatory and neuropathic pain can all be decreased or diminished by applying the local treatment of sodium ion channel blockers, which could be neurotoxins [4]. Therefore, the neurotoxins have recently been considered as the bases for development of new and more potent pain killer drugs.

Here, we have analyzed ion channel proteins and neurotoxins proteins from UniProt database [5]. We have applied the Resonant Recognition Model (RRM) [6-11], which proposes that activation of proteins is based on electromagnetic radiation of the certain frequency characterizing the specific biological function of proteins. Thus, by using the RRM, we can calculate characteristic electromagnetic frequency of the pain related ion channel activation and consequently propose that the TERP patches conductive imprint can interfere with this frequency.

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## II. METHODOLOGY – RESONANT RECOGNITION MODEL

The Resonant Recognition Model (RRM) is based on the findings that certain periodicities within the distribution of energy of delocalized electrons along protein/DNA molecules are critical for protein/DNA biological functions and/or interactions with their targets [6-8]. 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 and charge velocity [6-11].

The RRM enables the calculation of these spectral characteristics, by assigning each amino acid a physical parameter representing the energy of delocalized electrons of each amino acid. Comparing Fourier spectra for this energy distributions by using cross-spectral function, it has been found that proteins sharing the same biological function/interaction share the same periodicity (frequency) within energy distribution along the macromolecule [6,7]. Furthermore, it has been shown that interacting proteins and their targets share the same characteristic frequency, but have opposite phase at characteristic frequency [6-8]. Thus, it has been proposed that the RRM frequencies characterize, not only a general function, but also a recognition and interaction between the macromolecule and its target, which then can be considered as resonant recognition. This could be achieved with resonant energy transfer between the interacting macromolecules through oscillations of a physical field, which is 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  $7.87 \times 10^5 \text{ m/s}$  [6,7]. For this velocity and with the distance between amino acids in a protein molecule of  $3.8 \text{ \AA}$ , the frequency of protein interactions was estimated to be in the range between  $10^{13} \text{ Hz}$  and  $10^{15} \text{ Hz}$ . Therefore, the estimated frequency range for both amino acid and nucleotide macromolecules includes infra-red, visible and ultra-violet light. To support this idea, we compared our computational predictions with number of published experimental results [6,7]:

- Laser light growth promotion of cells, by using the specific 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 850-860nm;
- Activation of highly homologous plant photoreceptors which, although being very homologous, absorb different wavelengths of light;
- Photo activated 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  $K=201$  [6,7,11]. These 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  $\lambda$  is the wavelength of light irradiation in nm, which can influence specific biological process,  $f_{\text{rrm}}$  is a RRM numerical frequency and  $K$  is coefficient of this linear correlation.

We applied this concept on number of proteins and DNA examples [6-12]. The concept has been also experimentally tested by predicting the electromagnetic frequencies for L-Lactate Dehydrogenase [13], where by radiating L-Lactate Dehydrogenase with predicted calculated electromagnetic frequencies the significant change in enzyme activity was achieved. The concept has also been tested independently on experimental measurements of photon emission from dying melanoma cells [14], on photon emission from lethal and non-lethal Ebola strains [15], as well as on classic signaling pathway, JAK-STAT, traditionally composed of nine sequential protein interactions [16].

Keeping all this in mind, we propose that the RRM concept is excellent predictor for proteins and DNA selective interactions, biological processes and pathways in living cells. In our previous work, we have calculated large number of specific frequencies for different protein and DNA biological functions and interactions [11].

Frequencies calculated using the RRM, as described above, have been found to be related to biological function of the proteins [6-13]. However, if we consider protein and DNA complex structures, particularly alpha helices the charge transfer is also possible to occur through these structures in form of solitons [17] (Davydov [18,19], Hayman [20], Sinkala [21]), excitons (Davydov [18,19], Pang [22], Sinkala [21], Yomosa [23]) and phonons (Pang [22], Yomosa [23], Ichinose [24]). These other forms of charge transfers are at velocities different than initially used by the RRM and are ranging from  $10^5 \text{ m/s}$  for solitons and some excitons all the way down to speed of sound and small fractions of speed of sound for phonons. Thus, with the same periodicities within proteins sequences, as determined by the RRM, different modalities of charge transfer can produce different resonant frequencies which not necessarily are related to the protein biological function, but could be related to protein and DNA resonances in general.

In our previous work, we have applied all of this charge moving modalities to tubulin and microtubule macromolecules and identified number of possible electromagnetic resonance frequencies in these macromolecule structures [9]. These results have been experimentally confirmed in research by Bandyopadhyay [25]. Here, we applied this approach to pain related ion channel proteins with the aim to find out if there are possible resonances with these modalities that can resonate with TERP imprint frequencies.

## III. MATERIALS

In this work, we used protein sequences that form pain related sodium ion channels, pain related calcium ion channels, as well as toxins that can block and influence opening and closing of these pain related ion channels. We analyzed human, mouse and rat ion channels only, as they are mostly investigated and

mostly related to human pain. These protein sequences were used from UniProt Database [5]: twelve sodium ion channel proteins related to pain; three pain toxin proteins that influence opening and closing of sodium ion channels; fifteen mu-conotoxin proteins that also influence opening and closing of sodium ion channels; eight calcium ion channel proteins related to pain and eight omega-conotoxin proteins that influence opening and closing of calcium ion channels. All these protein sequences have been listed below:

twelve sodium ion channel proteins related to pain: (P35498-SCN1A\_HUMAN, A2APX8|CN1A\_MOUSE, Q99250-SCN2A\_HUMAN, Q9NY72-SCN3B\_HUMAN, Q8BHK2-SCN3B\_MOUSE, Q9JK00-SCN3B\_RAT, Q15858-SCN9A\_HUMAN, Q62205-SCN9A\_MOUSE, Q6QIY3-SCNAA\_MOUSE, Q62968-SCNAA\_RAT, Q9UI33-SCNBA\_HUMAN, O88457-SCNBA\_RAT);

three pain toxin proteins: (E7CAU3-SCU1\_MESMA, Q95P69-SCAA\_MESMA, P0CH40-CEII8\_CENEL);

fifteen mu-conotoxin proteins: (C1J5M6-CM3B\_CONBU, P01523-CM3A\_CONGE, P0C195-CM3A\_CONKI, P58925-CM3A\_CONPU, P60207-CM3A\_CONSE, Q86DU6-CM3A\_CONST, P0C350-CM3A\_CONTU, C1J5M6-CM3B\_CONBU, C1J5M7-CM3C\_CONBU, P58926-CM4A\_CONPE, P58927-CM4B\_CONPE, P0DKQ9-CM31\_CONTU, I1SB07-GM3C\_CONCN, P56708-CO6A\_CONMR, Q26443-CO16B\_CONMR);

eight calcium ion channel proteins related to pain: (O00555-CAC1A\_HUMAN, P97445-CAC1A\_MOUSE, P54282-CAC1A\_RAT, Q00975-CAC1B\_HUMAN, O55017-CAC1B\_MOUSE, Q02294-CAC1B\_RAT, Q61290-CAC1E\_MOUSE, Q9EQ60-CAC1H\_RAT);

eight omega-conotoxin proteins: (P58914-CO6A\_CONRA, P58915-CO6A\_CONTU, P56713-CO6B\_CONPE, P56714-CO7\_CONTE, P01522-CO16A\_CONGE, P28880-CO16A\_CONST, P58920|CO16D\_CONCT, P05484-CO17A\_CONMA).

#### IV. RESULTS

When twelve sodium pain related ion channel proteins have been compared using the RRM model, two distinct common RRM frequencies have been identified:  $fn1=0.1465$  and  $fn2=0.1567$ , presented as two peaks within the RRM cross-spectrum in Figure 1. These two frequencies could be attributed to the two main functions of sodium ion channels: first function forming the ion channel itself by getting number of channel proteins together into the channel structure and second function performing opening and closing of ion channels. This second function is of our interest, as opening and closing of ion channels controls transport of ions across the neuron cell membrane and thus controls cell activation potential, that is essential for pain signal to travel along the

nerve (axon). To identify which of these two frequencies is related to opening and closing of ion channels, we have compared RRM cross-spectrum of sodium ion channel proteins with toxin proteins that block these opening and closing of ion channels. According to RRM principles [6,7], it is expected that these toxin proteins would have the same RRM frequency as opening and closing frequency within the sodium ion channels. These toxin proteins, because of their influence on ion channels, are also candidate substances for production of relevant pain killers. The group of toxin proteins we have selected are three pain toxins and fifteen mu-conotoxins. When pain related sodium channels are compared with pain toxins the frequency  $fn1=0.1465$  has become more prominent, as presented in Figure 2. When mu-conotoxins are added to this comparison only  $fn1=0.1465$  has been left prominent, as presented in Figure 3. These results according to the RRM principles [6,7], revealed the frequency  $fn1=0.1465$ , can be attributed to the function of opening and closing pain related sodium ion channels.

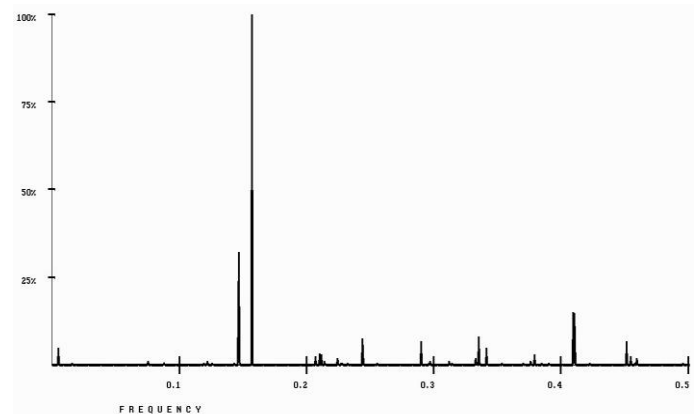


Fig. 1 RRM cross-spectrum of twelve sodium ion channel proteins. X-axis represents numerical RRM frequencies, while Y-axis represents percentage relative to maximum amplitude in cross-spectrum.

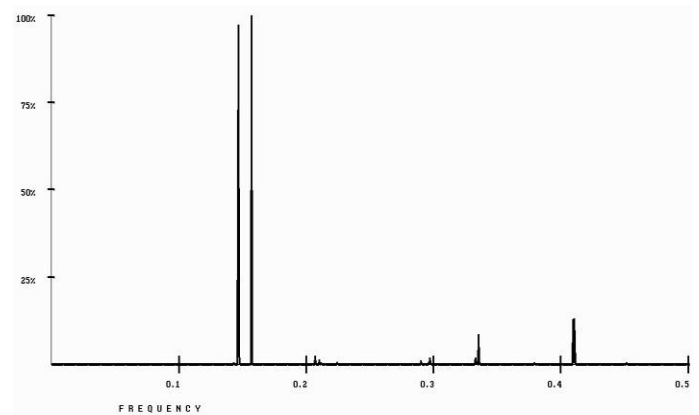


Fig. 2 RRM cross-spectrum of twelve sodium ion channel proteins and three pain toxins. X-axis represents numerical RRM frequencies, while Y-axis represents percentage relative to maximum amplitude in cross-spectrum.

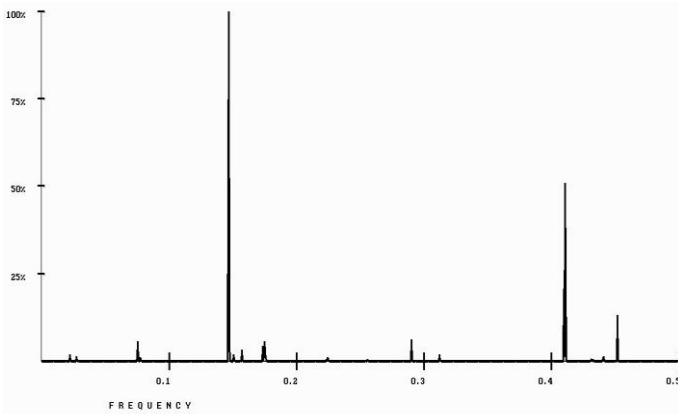


Fig. 3 RRM cross-spectrum of twelve sodium ion channel proteins, three pain toxins and fifteen mu-conotoxins. X-axis represents numerical RRM frequencies, while Y-axis represents percentage relative to maximum amplitude in cross-spectrum.

Once when this characteristic RRM frequency was identified, we can calculate relevant wavelength of related electromagnetic radiation using the formula, as explained above:

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

The wavelength related to the frequency relevant for opening and closing pain related sodium ion channels is then  $\lambda=1372\text{nm}$ . Therefore, we propose that Titanium Salt particles and imprints in the TERP patches, which are conductive and are in diameter/length of about  $D\lambda=1400\text{nm}$ ,  $D\lambda/2=700\text{nm}$  and  $D\lambda/4=350\text{nm}$ , can resonantly absorb and damp electromagnetic radiation from ion channel activation [6,7,10-16]. This implies that, such resonance can interfere with activity of pain related sodium ion channels, influence their opening and closing function and consequently influence pain transmission along the nerve (axon).

When eight calcium pain related ion channel proteins have been compared using the RRM model two distinct common RRM frequencies have been identified:  $fc1=0.0002$  and  $fc2=0.1021$ , presented as two peaks within the RRM cross-spectrum in Figure 4. These two frequencies could be attributed to the two main functions of calcium ion channels: first function forming the ion channel itself by getting number of channel proteins together into the channel structure and second function performing opening and closing of ion channels. This second function is of our interest, as opening and closing of ion channels controls transport of ions across the neuron cell membrane and thus controls cell activation potential, that is essential for pain signal to travel along the nerve (axon). To identify which of these two frequencies is related to opening and closing of ion channels, we have compared RRM cross-spectrum of calcium ion channel proteins with toxin proteins that block these opening and closing of ion channels. According to RRM principles [6,7], it is expected that these toxin proteins would have the same RRM frequency as opening and closing frequency within the calcium ion channels. These toxin proteins, because of their influence on ion channels, are also candidate substances for production

of relevant pain killers. The group of toxin proteins we have selected are eight omega-conotoxins. When pain related calcium channels are compared with omega conotoxins only the frequency  $fc2=0.1021$  has become prominent, as presented in Figure 5. These results according to the RRM principles, revealed the frequency  $fc2=0.1021$ , can be attributed to the function of opening and closing pain related calcium ion channels.

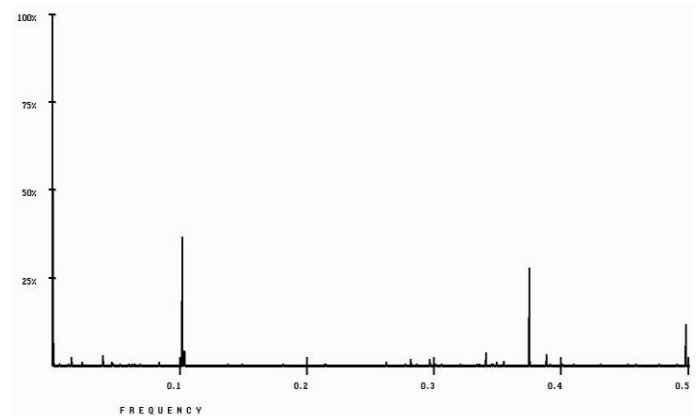


Fig. 4 RRM cross-spectrum of eight calcium ion channel proteins. X-axis represents numerical RRM frequencies, while Y-axis represents percentage relative to maximum amplitude in cross-spectrum.

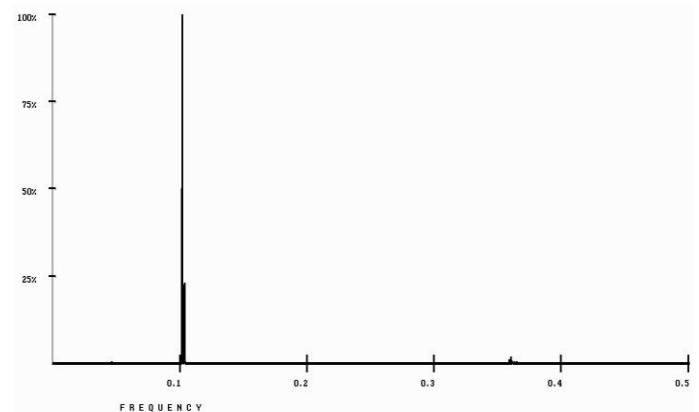


Fig. 5 RRM cross-spectrum of eight calcium ion channel proteins and eight omega-conotoxins. X-axis represents numerical RRM frequencies, while Y-axis represents percentage relative to maximum amplitude in cross-spectrum.

Once when this characteristic RRM frequency was identified, we can calculate relevant wavelength of related electromagnetic radiation using the formula, as explained above:

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

The wavelength related to the frequency relevant for opening and closing pain related sodium ion channels is then  $\lambda=1968\text{nm}$ . Therefore, we propose that Titanium Salt particles and imprints in the TERP patches, which are conductive and are in diameter/length of about  $D\lambda=2000\text{nm}$ ,  $D\lambda/2=1000\text{nm}$  and  $D\lambda/4=500\text{nm}$ , can resonantly absorb and damp electromagnetic radiation from ion channel activation [6,7,10-16]. This implies that, such resonance can interfere with

activity of pain related sodium ion channels, influence their opening and closing function and consequently influence pain transmission along the nerve (axon).

To find out, if there are other resonant electromagnetic frequencies that can influence pain related to ion channels, we have introduced other modalities of charge transfer through proteins (solitons, excitons and phonons), as described above. We have started from RRM characteristic frequencies identified to be related to opening and closing pain related ion channels,  $f_{n1}=0.1465$  for sodium ion channels and  $f_{c2}=0.1021$  for calcium ion channels. When different modalities of charge transfer were applied to two RRM frequencies the following resonant frequencies have been identified for each modality, as presented in Table I.

TABLE I  
ELECTROMAGNETIC FREQUENCIES FOR DIFFERENT MODALITIES

RRM Frequency	Sodium: 0.1465	Calcium: 0.1021
velocity as per RRM $7.87 \times 10^5$ m/s [6]	151-152THz	105-106THz
velocity as per Yomosa 3.2m/s [23]	614-619MHz	428-432MHz
velocity as per Yomosa $1.2 \times 10^5$ m/s [23]	23-23THz	16-16THz
velocity as per Pang 68m/s [22]	13-13GHz	9-9GHz
velocity as per Davydov 170m/s [18,19]	33-33GHz	23-23GHz
velocity as per Ichinose 0.34m/s [24]	65-66MHz	45-46MHz
velocity as per Ichinose $5 \times 10^{-4}$ m/s [24]	96-97KHz	67-67KHz

These frequencies are proposed to be able to resonate with pain related ion channels and may influence their function. Here, we propose that if these frequencies are imprinted in TERP patches then such TERP's can resonate with pain related ion channels. According to RRM principles [6,7], all these results could explain the mechanisms how TERP patches remediate the pain.

## V. CONCLUSION

In this study, we have analyzed pain related sodium and calcium ion channels, using the RRM model, with the aim to find the characteristic resonant frequencies for opening and closing of these ion channels and to investigate possibility of these frequencies to resonate with frequencies imprinted within TERP patches and consequently to propose mechanism of pain relieve by using the TERP patches.

We found that:

- Characteristic frequency for pain related sodium ion channel opening and closing function is  $f_{n1}=0.1465$ . This numerical RRM frequency relates to electromagnetic wavelength  $\lambda=1372$ nm. Therefore, the Titanium Salt particles and imprints in the TERP patches, which are conductive and are in diameter/length of about  $D\lambda=1400$ nm,  $D\lambda/2=700$ nm and  $D\lambda/4=350$ nm, can resonantly absorb and damp electromagnetic radiation from ion channel activation. This implies that, such resonance can interfere with activity of pain related sodium ion channels, influence their opening and closing function and consequently influence pain transmission along the nerve (axon);

- Characteristic frequency for pain related calcium ion channel opening and closing function is  $f_{c2}=0.1021$ . This numerical RRM frequency relates to electromagnetic wavelength  $\lambda=1968$ nm. Therefore, the Titanium Salt particles and imprints in the TERP patches, which are conductive and are in diameter/length of about  $D\lambda=2000$ nm,  $D\lambda/2=1000$ nm and  $D\lambda/4=500$ nm, can resonantly absorb and damp electromagnetic radiation from ion channel activation. This implies that, such resonance can interfere with activity of pain related sodium ion channels, influence their opening and closing function and consequently influence pain transmission along the nerve (axon);

- When different modalities of charge transfer through protein backbone are introduced [9,10], the resonant frequencies for sodium and calcium ion channels could then be in different frequency ranges including THz, GHz, MHz and KHz, as presented in Table I. These frequencies could also resonate with frequency imprinted within TERP patches. Thus, with the same periodicities within proteins sequences, as determined by the RRM, different modalities of charge transfer can produce different resonant frequencies which are not necessarily related to the protein biological function, but could be related to ion channel resonances in general.

All these findings could explain mechanisms of TERP patches for relieving the pain through the resonances with pain related ion channels. This would mean that TERP patches could mimic similar activity as toxin based pain killers, but without side effects.

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