Detection of Milimeter Wave Properties of Beta Amyloid using Dielectric Filled Truncated Cylindrical Waveguide

Komal Saxena*(1), Zeeshan(1), Mridul Kumar(1), K. S. Daya(1), Anirban Bandyopadhyay(2)
(1) 1Microwave Physics Laboratory, Department of Physics and Computer Science, Dayalbagh Educational Institute, Dayalbagh, Agra-282005, Uttar Pradesh, India, https://www.dei.ac.in/
(2) National Institute for Materials Science, Advanced Key Technologies Division, 1-2-1 Sengen, Tsukuba, Ibaraki-3050047, Japan

Abstract

Alzheimer's disease (AD) is most common type of degenerative disorder, which is associated with the extracellular aggregation of beta-amyloid plaques [1] and intracellular neurofibrillary beta tangles [2] in the brain. Aggregation of amyloid and tangles from nm to hundred of μm range make them exciting for studying the dielectric properties [3]. These properties change as beta-amyloid and tangles are exposed to the external stimulus. In this paper, transmission properties of beta amyloid have been experimentally analyzed using dielectric filled truncated cylindrical sensor at different microwave frequency up to 30 GHz. Fundamental frequency of the sensor is 5.6 GHz. To perturb the beta-amyloid, we have used ultra low frequency electric field as external stimuli. It has been reported that diseases could be cured by exposing the associated biomolecules into an electric field. Therefore this study can be helpful for the AD treatment by perturbing its dielectric properties.

Keywords— Alzheimer's disease; beta-amyloid plaques; dielectric filled truncated cylindrical sensor; neurofibrillary beta tangles; sensor.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by short term memory loss and alteration of cognitive abilities. With increasing human age, brain has slow decline process in memory, thinking and skills [1] [2]. However, despite the extensive research in this field, scientists have not completely understood the cause of its origin. Probable causes of this disease include the genetic, cellular and molecular imbalance [3]. The aggregation of extracellular beta amyloid plaques [4] and intracellular neurofibrillary tangles [5], which contain the microtubule associated protein tau [6] in hyperphosphorylated state belong to the category of molecular imbalance. Disassemblies of microtubules in AD have also been reported [7] [8]. Microtubule stabilizing drugs affect the dynamic stability and assemblies of microtubule. Recent evidences suggest that very low doses of microtubule- stabilizing drugs may be helpful to reverse Aβ-induced loss of synaptic connectivity in early staged AD. This is the very specific controlled modulation of microtubule dynamics in cell that gives valuable target to prevent neurodegenerative processes in AD [8].

Tremendous research on the interaction of electromagnetic radiation on the bio-systems at several levels from macromolecules to a living organism is reported [9]. The dynamic nature of bio-systems is the key factor of chemical and electrical interaction between the cells [8 – 12]. But external stimulus like electric field, light, drugs and temperature also affect the cellular interaction of bio-systems [13 – 18]. Unique signature of aggregation and dispersion of biomolecules from nm to hundreds of μm make them particularly interesting for carrying out the dielectric studies [13 – 18]. High frequency resonance of biomolecules motivates to explore the dielectric properties of beta Amyloid in the gigahertz frequency region. Here we examined the transmission properties of beta Amyloid using cost effective and label free sensor at microwave frequency. The designing of sensor is based on the dielectric filled truncated cylindrical waveguide having the cut-off frequency of 5.6 GHz. Further we examined the effect of external low frequency field on the resonant frequencies of beta Amyloid.

2. Interaction of the Biomolecules with Electromagnetic Field

Interactions of EM fields with biomolecules at high frequencies create interesting primary and secondary effects, which has led to many applications. The aggregations of biomolecules lead to the redistribution of water surrounding these biomolecules. Therefore, ambient water plays a crucial role in biomolecules dynamics [18] [19] [20]. It generates intrinsic resonance when exposed to weak EM field in the gigahertz frequency range. At these frequencies, water-molecule oscillators lock on the external signal. These locked standing waves can penetrate deep into the system and can be an effective probe for information mining or manipulation [11] [18]. This information is useful for studying the dielectric properties of biomolecules. Permittivity is the measure of the dielectric properties of the material. When the material is exposed to an electric field, the resonant frequencies of the material change. Propagation wavelength in a dielectric medium is reduced by a factor $(\mathcal{E})^{1/2}$.

$$f = \frac{c}{\lambda\sqrt{\mathcal{E}}} \qquad (1).$$

Structure and geometry of beta amyloid plaque may also be responsible for this interaction. The slow varying electromagnetic field is able to interact with the pinned high frequency fields between the teeth of comb like geometry and cascading down a macroscopic effect on the overall electrical properties of the biological system.

3. Experimental Setup

The designing of the sensor is based on the dielectric filled truncated cylindrical waveguide. This waveguide is filled with Teflon having the relative permittivity of 2.1. Inner and outer diameter of the Teflon cylinder is 2 mm and 4 mm respectively. It is partially coated with the copper tape, which guides the propagation of the wave. The thickness of the copper tape is .135 mm. Truncated gap between the walls is 1 mm. This gap causes the coupling of electromagnetic wave at this place. In between the gap there is a small aperture, which is helpful for loading the sample. The cut-off frequency of the sensor is 5.6 GHz. The sensor is placed in the aluminium cavity to minimize the conductor losses. Wave is coupled using loop antennas of 1 mm diameter. The entire setup is connected to the ZVA 50 Vector Network Analyzer (VNA) for measuring the scattering parameters. Apart from this the setup includes the function generator to give the external stimuli to the system.

4. Results and Discussion

Experimental observations of scattering parameter have been carried out using Rohde & Schwarz ZVA 50 vector network analyzer. The resonance frequencies and corresponding quality factors of the sensor have been measured at different values in the millimeter wave region. Here we have selected five values of resonant frequencies in microwave range up to 30 GHz for our experiment. Microwave-based detection sensor is reusable and low cost method of measuring biomolecules in micrometer scale with high sensitivity and accuracy. On loading the beta amyloid in the sensor, its capacitance and inductance sensitivity increases in gigahertz frequency, [21] resulting in the significant changes in resonance frequencies. Loaded and unloaded sample data up to 30 GHz are shown in figure 3.

For the unloaded and loaded sensor, experimentally measured quality factors and resonant frequencies have been compared in table 1. It is clear from the tabular data that the resonant frequencies are shifted downward after

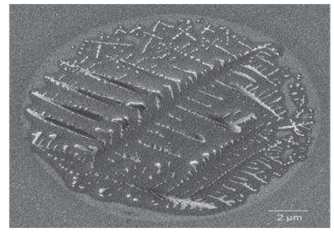

Figure 1. Helium ion microscope image of beta amyloid. Here teeth of comb like geometry of beta amyloid is clearly seen.

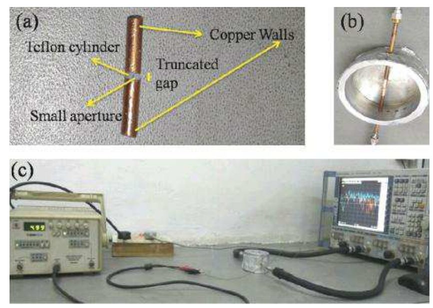

Figure 2. (a) Proposed sensor based on dielectric filled truncated cylindrical. Here sample is loaded through small aperture in the waveguide. It is made up of the Teflon cylinder, which is partially coated with the copper tape. (b) Dielectric filled truncated cylindrical waveguide is placed in the aluminum cavity for minimizing the losses. It is coupled to external circuit using loop antenna. (c) The entire setup is connected to VNA for measuring the resonant properties in gigahertz range. Further for measuring the effect of low frequency field on the resonant frequencies, we give the external stimulus from the function generator.

loading the sample due to the dielectric perturbation. From the loaded Q factor we can calculate the relaxation time, which is illustrated in figure 4.

$$Ql = 2\pi f \tau \qquad (2).$$

Where, Q_l is the loaded quality factor of the sample. τ is the relaxation time. Relaxation time is the time in which the system returns from perturbed state to the equilibrium state. Due to having the dominating constituent (55% - 75%) of water in biological materials, it has its own importance while studying the dielectric properties. It has been reported that the relaxation frequency of water is 17 GHz i.e. τ is in the fraction of nano-sec [22]. Figure 4 shows that relaxation time of beta amyloid is about 100 times higher than the relaxation time of water, which means that amyloid takes a long time to become neutral in molecular polarization.

Table 1. Comparison of Experimental Results for the Unloaded and Loaded Sensor

Unloaded		**Loaded**	
Resonant Frequency (GHz)	***Q Factor***	***Resonant Frequency (GHz)***	***Q Factor***
5.563	55.561	5.488	40.466
7.308	160.136	7.288	139.462
17.533	749.522	17.527	793.395
20.743	1177.603	20.739	721.078
21.698	510.540	21.696	501.552

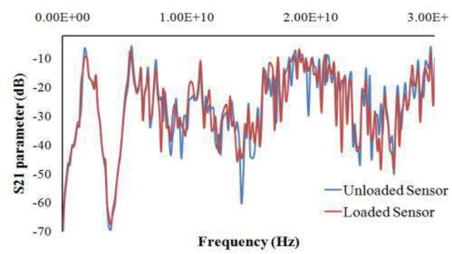

Figure 3. Resonance of Beta Amyloid upto 30 GHz**.**

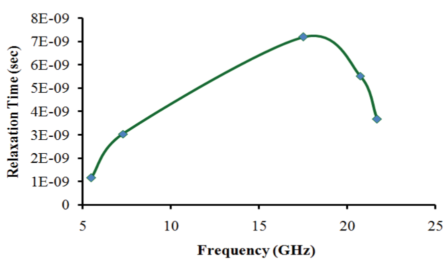

Figure 4. Relaxation time at the resonant frequecies of beta amyloid.

By applying the external field, material gets perturbed. Polarisation and dipole take place in the molecules. The group of molecular dipoles is large compared to the radiating wavelength of EM wave. However, coupling and energy transfer of an EM wave to cellular structures can be effective through resonant interaction of the EM field with vibration modes of the cellular structures. As we discussed earlier that interaction of slow varying field with the beta amyloid can be possible due to having the teeth of comb like geometry.

This slow varying field effect is also observed by applying the low frequency field from the function generator. Effect of low varying electric field from 1 Hz to 5 Hz on the resonance frequencies of microtubule is presented in figure 5.

5. Conclusion

Nowadays AD has become one of the most significant health problems. This disease occurs due to disorganization of neuronal microtubule, aggregation of amyloid plaques and neurofibrillary tangles in brain. Here we experimentally analyzed the transmission properties of beta amyloid at microwave frequency using dielectric filled truncated cylindrical sensor. Further, this explorative experiment study shows that perturbing the beta plaque coupled at microwave frequencies with ultra low frequency electric fields can influence the polarization ability and can make the beta plaque less resistive to the applied field or more conducting.

Acknowledgements
We thank Dr. Anirban Bandyopadhyay for allowing to work on the helium ion microscope at National Institute for Material Science, Japan.

6. References

1. A. S. Henderson, and A. F. Jorm, “Definition, and Epidemiology of Dementia: A Review,” in Denmentia, Eds. M. Maj and N. Sartorius, John Wiley & Sons, Ltd, UK, 2002.
2. Son Tung Ngo, “Interactions between small molecules and amyloid beta peptides: Implications for Alzheimer's disease,” Doctor of Philosophy thesis, Institute of Physics Polish Academy of Sciences, 2015.
3. Karl Herrup, “The case for rejecting the amyloid cascade hypothesis,” Nature Neurosciene **18**, pp. 794 – 799, 2015.
4. J. Hardy, and D. J. Selkoe, “The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics,” Science **297**, pp. 353—356, 2002.
5. Alejandra D. C. Alonso, I. Grundke-Iqbal, and K. Iqbal, “Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules,” Nature Medicine **2**, pp. 783 – 787, 1996.
6. M. Kolarova, F. Garcia-Slerra, A. Bartos, J. Ricny, and D. Ripova, “Structure and Pathology of Tau Protein in Alzheimer Disease,” International Journal of Alzheimer’s Disease **2012**, pp. 1 – 13, 2012.
7. Iqbal, K., T. Zaidi, G. Y. Wen, I. G. Iqbal, P. A. Merz, S. S. Shaikh, H. M. Wisniewski, I. Alafuzoff, and B. Winblad, “Defective brain microtubule assembly in Alzheimer’s disease,” The Lancet **328**, pp. 421 – 426, 1986.
8. Brandt, Roland, and Lidia Bakota, "Microtubule dynamics and the neurodegenerative triad of Alzheimer's disease: The hidden connection," Journal of neurochemistry **143,** pp. 409 – 417, 2017.
9. J. A. Marc Brown, “A Study of the Interactions between Electromagnetic Fields and Microtubules: Ferroelect ric Effects, Signal Transduction and Electronic Conduct ion,” Doctor of Philosophy thesis, University of Alberta, 1999.
10. Y. K. Al-Hilaly, S. J. Pollack, D. M. Vadukul, F. Citossi, J. E. Rickard, M. Simpson, J. M. D. Storey, C. R. Harrington, C. M. Wischik, and L. C. Serpell, “Alzheimer's Disease-like Paired Helical Filament Assembly from Truncated Tau Protein Is Independent of

Disulfide Crosslinking," J Mol Biol **429,** pp. 3650 – 3665, 2017.

11. M. Cifra, Jeremy Z. Fields, and Ashkan Farhadi. "Electromagnetic cellular interactions." Progress in biophysics and molecular biology **105,** pp. 223 – 246, 2011.

12. J. Pokorný, K. Vacek, J. Fiala, "Fröhlich electromagnetic fields generated by living cells: computer results," Journal of Biological Physics **12**, pp. 79 – 84, 1984.

13. Setayandeh, S. S., and A. Lohrasebi, "Influence of GHz electric fields on the mechanical properties of a microtubule," J. Mol. Model **21**, pp. 1–7, March 2015.

14. Kirson, E.D., Gurvich, Z., Schneiderman, R., Dekel, E., Itzhaki, A., Wasserman, Y., Schatzberger, R., Palti, Y., "Disruption of cancer cell replication by alternating electric fields," Cancer Res. **64**, pp. 3288–3295, 2004.

15. Zaremba, T. G., Thomas R. LeBon, David B. Millar, Ruthann M. Smejka1, and Robert J. Hawley, "Effects of Ultraviolet Light on the in Vitro Assembly of Microtubules," Biochemistry **23**, No. 6, pp. 1073 – 1080, 1984.

16. R., Veselská and Janisch R., "The Effect of UV Irradiation on Changes in Cytoskeleton and Viability of Mouse Fibroblasts L929 Cell Line," Scripta Medica (BRNO) **73**, No. 6, pp. 393 – 408, 2000.

17. Dye, R. B., "Taxol-induced Flexibility of Microtubules and Its Reversal by MAP-2 and Tau," The Jour. Of Biol. Chem **268**, No. 10, pp. 6847 – 6850, 1993.

18. Sahu, Satyajit, Subrata Ghosh, Daisuke Fujita, and Anirban Bandyopadhyay, "Live visualizations of single isolated tubulin protein self-assembly via tunneling current: effect of electromagnetic pumping during spontaneous growth of microtubule," Scientific Reports, **4**: pp. 7303, 1–9, December 2014.

19. Donald E. Barry, Jr., "Studies of Aggregation Pathways for Amyloidogenic Peptides by Dielectric Relaxation Spectroscopy," Doctor of Philosophy thesis, Worcester Polytechnic Institute, 2013.

20. P. W. Fenimore, H. Frauenfelder, B. H. McMahon, and F. G. Parak, "Slaving: Solvent fluctuations dominate protein dynamics and functions," Proceedings of the National Academy of Sciences **99,** pp. 16047 – 16051, 2002.

21. M. Nikolic-Jaric, S. F. Romanauik, G. A. Ferrier, G. E. Bridges, M. Butler, K. Sunley, D. J. Thomson, and M. R. Freeman, "Microwave frequency sensor for detection of biological cells in microfluidic channels," Biomicrofluidics **3**, pp. 034103: 1-15, 2009.

22. Subhajit Guha, Farabi Ibne Jamal, Christian Wenger, "A Review on Passive and Integrated Near-Field Microwave Biosensors," Biosensor **7**, pp 1-18, 2017.

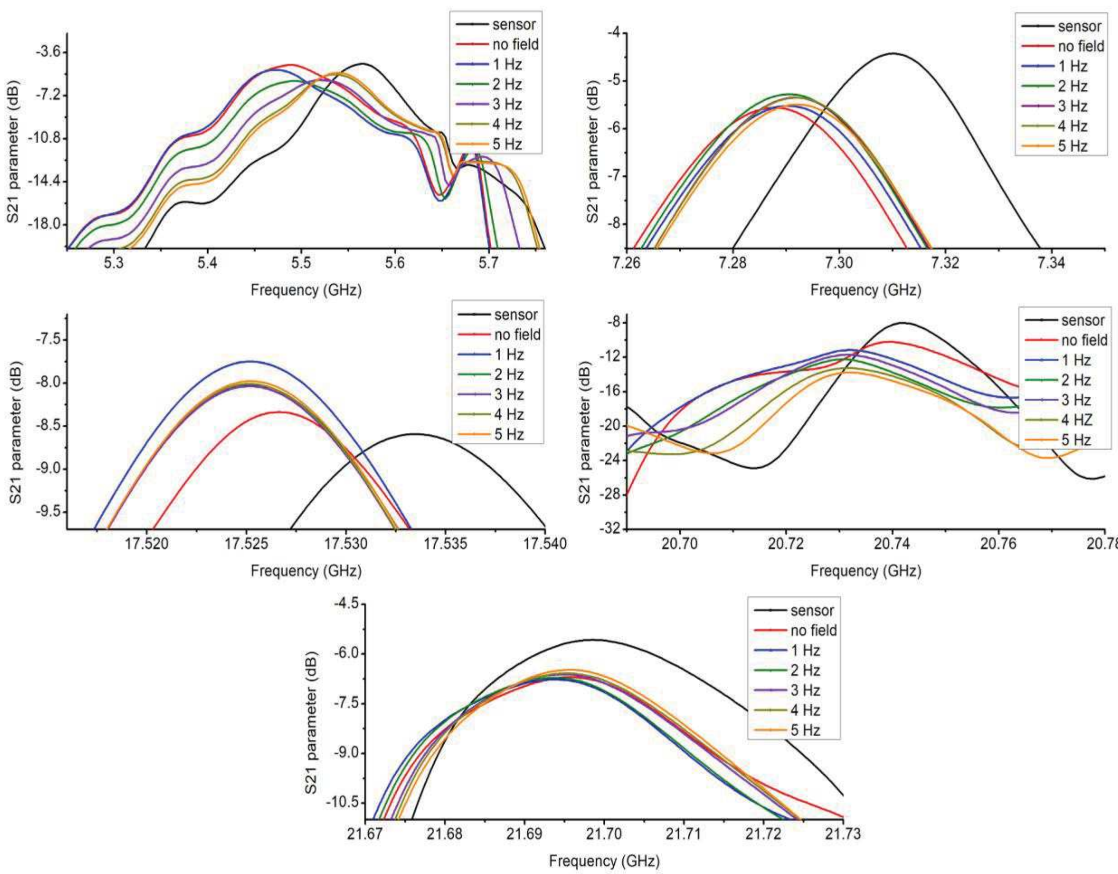

Figure 5. Effect of external low frequency field on the resonance of beta amyloid at (a) 5.563 GHz (b) 7.308 GHz (c) 17.533 GHz (d) 20.743 GHz (e) 21.698 GHz.